

PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF CNS AND OTHER  
DISORDERS

Background of the Invention

5 The present invention relates to a method of treating disorders of the central nervous system (CNS) and other disorders in a mammal, including a human, by administering to the mammal a CNS-penetrant alpha-7 ( $\alpha 7$ ) nicotinic receptor agonist. It also relates to pharmaceutical compositions containing a pharmaceutically acceptable carrier and a CNS-penetrant alpha-7 nicotinic receptor agonist.

10 Schizophrenia is characterized by some or all of the following symptoms: delusions (i.e., thoughts of grandeur, persecution, or control by an outside force), auditory hallucinations, incoherence of thought, loss of association between ideas, marked poverty of speech, and loss of emotional responsiveness. Schizophrenia has long been recognized as a complex disease, which to date has eluded biochemical or genetic characterization. However, recent data in the literature suggest that alpha-7 nicotinic receptor agonists may be  
15 therapeutic for this, and other CNS disorders, see: Alder, L.E.; Hoffer, L.D.; Wiser, A.; Freedman, R. Am. J. Psychiatry 1993, 150, 1856; Bickford, P.C.; Luntz-Leybman, V.; Freedman, R. Brain Research, 1993, 607, 33; Stevens, K.E.; Meltzer, J.; Rose, G.M. Psychopharmacology 1995, 119, 163; Freedman, R.; Coon, H.; Myles-Worsley, M.; Orr-Urtreger, A.; Olincy, A.; Davis, A.; Polymeropoulos, M.; Holik, J.; Hopkins, J.; Hoff, M.;  
20 Rosenthal, J.; Waldo, M.C.; Reimherr, F.; Wender, P.; Yaw, J.; Young, D.A.; Breese, C.R.; Adams, C.; Patterson, D.; Alder, L.E.; Kruglyak, L.; Leonard, S.; Byerley, W. Proc. Nat. Acad. Sci. USA 1997, 94, 587.

The compositions of the present invention that contain an alpha-7 nicotinic receptor agonist are useful for the treatment of depression. As used herein, the term "depression"  
25 includes depressive disorders, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, anxiety and phobias, seasonal  
30 affective disorder, or bipolar disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder.

Other mood disorders encompassed within the term "depression" include dysthymic disorder with early or late onset and with or without atypical features; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with  
35 depressed mood, mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances;

schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood.

The compositions of the present invention that contain an alpha-7 nicotinic receptor agonist are useful for the treatment of anxiety. As used herein, the term "anxiety" includes anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalized anxiety disorders.

"Generalized anxiety" is typically defined as an extended period (e.g. at least six months) of excessive anxiety or worry with symptoms on most days of that period. The anxiety and worry is difficult to control and may be accompanied by restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and disturbed sleep.

"Panic disorder" is defined as the presence of recurrent panic attacks followed by at least one month of persistent concern about having another panic attack. A "panic attack" is a discrete period in which there is a sudden onset of intense apprehension, fearfulness or terror. During a panic attack, the individual may experience a variety of symptoms including palpitations, sweating, trembling, shortness of breath, chest pain, nausea and dizziness. Panic disorder may occur with or without agoraphobia.

"Phobias" includes agoraphobia, specific phobias and social phobias. "Agoraphobia" is characterized by an anxiety about being in places or situations from which escape might be difficult or embarrassing or in which help may not be available in the event of a panic attack. Agoraphobia may occur without history of a panic attack. A "specific phobia" is characterized by clinically significant anxiety provoked by feared object or situation. Specific phobias include the following subtypes: animal type, cued by animals or insects; natural environment type, cued by objects in the natural environment, for example storms, heights or water; blood-injection-injury type, cued by the sight of blood or an injury or by seeing or receiving an injection or other invasive medical procedure; situational type, cued by a specific situation such as public transportation, tunnels, bridges, elevators, flying, driving or enclosed spaces; and other type where fear is cued by other stimuli. Specific phobias may also be referred to as simple phobias. A "social phobia" is characterized by clinically significant anxiety provoked by exposure to certain types of social or performance circumstances. Social phobia may also be referred to as social anxiety disorder.

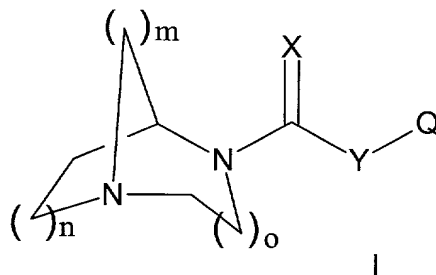
Other anxiety disorders encompassed within the term "anxiety" include anxiety disorders induced by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, phencyclidine, sedatives, hypnotics, anxiolytics and other substances, and adjustment disorders with anxiety or with mixed anxiety and depression.

Anxiety may be present with or without other disorders such as depression in mixed anxiety and depressive disorders. The compositions of the present invention are therefore useful in the treatment of anxiety with or without accompanying depression.

By the use of a CNS-penetrant alpha-7 nicotinic receptor agonist in accordance with the present invention, it is possible to treat depression and/or anxiety in patients for whom conventional antidepressant or antianxiety therapy might not be wholly successful or where dependence upon the antidepressant or antianxiety therapy is prevalent.

### Summary of the Invention

This invention relates to compounds of the formula I



wherein  $n = 1-2$ ;

$m = 1-2$ ;

$o = 1-2$ ;

$X = O, S, \text{ or } NR^1$ ;

$Y = O, S, \text{ or } NR^1$ ;

$R^1$  is H, a straight chain or branched  $(C_1-C_8)$ alkyl,  $-C(=O)OR^6$ ,  $-CH_2R^6$ ,  $-C(=O)NR^6R^7$ ,  $-C(=O)R^6$ , or  $-SO_2R^6$ ;

$Q$  is a straight chain or branched  $(C_1-C_8)$ alkyl, a straight chain or branched  $(C_2-C_8)$ alkenyl, a straight chain or branched  $(C_2-C_8)$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_8)$ cycloalkenyl, 3-8 membered heterocycloalkyl,  $(C_5-C_{11})$ bicycloalkyl,  $(C_7-C_{11})$ bicycloalkenyl, 5-11 membered heterobicycloalkyl, 5-11 membered heterobicycloalkenyl,  $(C_6-C_{11})$  aryl or 5-12 membered heteroaryl; wherein  $Q$  is optionally substituted with one to six substituents  $R^2$  independently selected from H, F, Cl, Br, I, nitro, cyano,  $CF_3$ ,  $-NR^3R^4$ ,  $-NR^3C(=O)R^4$ ,  $-NR^3C(=O)NR^4R^5$ ,  $-NR^3S(=O)_2R^4$ ,  $-NR^3S(=O)_2NR^4R^5$ ,  $-OR^3$ ,  $-OC(=O)R^3$ ,  $-OC(=O)OR^3$ ,  $-OC(=O)NR^3R^4$ ,  $-OC(=O)SR^3$ ,  $-C(=O)OR^3$ ,  $-C(=O)R^3$ ,  $-C(=O)NR^3R^4$ ,  $-SR^3$ ,  $-S(=O)R^3$ ,  $-S(=O)_2R^3$ ,  $-S(=O)_2NR^3R^4$ , and  $R^3$ ;

each  $R^3$ ,  $R^4$ , and  $R^5$  is independently selected from H, straight chain or branched  $(C_1-C_8)$ alkyl, straight chain or branched  $(C_2-C_8)$ alkenyl, straight chain or branched  $(C_2-C_8)$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_8)$ cycloalkenyl, (3-8 membered) heterocycloalkyl,  $(C_5-$

$C_{11}$ )bicycloalkyl,  $(C_7-C_{11})$ bicycloalkenyl, 5-11 membered heterobicycloalkyl, 5-11 membered heterobicycloalkenyl,  $(C_6-C_{11})$  aryl and 5-12 membered heteroaryl; wherein  $R^3$ ,  $R^4$ , and  $R^5$ , when not = H, are each independently optionally substituted with from one to six substituents, independently selected from F, Cl, Br, I, nitro, cyano,  $CF_3$ ,  $-NR^6R^7$ ,  $-NR^6C(=O)R^7$ ,  $-NR^6C(=O)NR^7R^8$ ,  $-NR^6S(=O)_2R^7$ ,  $-NR^6S(=O)_2NR^7R^8$ ,  $-OR^6$ ,  $-OC(=O)R^6$ ,  $-OC(=O)OR^6$ ,  $-OC(=O)NR^6R^7$ ,  $-OC(=O)SR^6$ ,  $-C(=O)OR^6$ ,  $-C(=O)R^6$ ,  $-C(=O)NR^6R^7$ ,  $-SR^6$ ,  $-S(=O)R^6$ ,  $-S(=O)_2R^6$ ,  $-S(=O)_2NR^6R^7$ , straight chain or branched  $(C_1-C_8)$ alkyl, straight chain or branched  $(C_2-C_8)$ alkenyl, straight chain or branched  $(C_2-C_8)$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_8)$ cycloalkenyl, 3-8 membered heterocycloalkyl,  $(C_5-C_{11})$ bicycloalkyl,  $(C_7-C_{11})$ bicycloalkenyl, 5-11 membered heterobicycloalkyl, 5-11 membered heterobicycloalkenyl,  $(C_6-C_{11})$  aryl, 5-12 membered heteroaryl, and  $R^6$ ;

or, when  $R^3$  and  $R^4$  are as in  $NR^3R^4$ , they may instead optionally be connected to form with the nitrogen of  $NR^3R^4$  to which they are attached a heterocycloalkyl moiety of from three to seven ring members, said heterocycloalkyl moiety optionally comprising one or two further heteroatoms independently selected from  $NR^5$ , O, S;

each  $R^6$ ,  $R^7$ , and  $R^8$  is independently selected from H, straight chain or branched  $(C_1-C_8)$ alkyl, straight chain or branched  $(C_2-C_8)$ alkenyl, straight chain or branched  $(C_2-C_8)$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_8)$ cycloalkenyl, 3-8 membered heterocycloalkyl,  $(C_5-C_{11})$ bicycloalkyl,  $(C_7-C_{11})$ bicycloalkenyl, 5-11 membered heterobicycloalkyl, 5-11 membered heterobicycloalkenyl,  $(C_6-C_{11})$  aryl and (5-12 membered heteroaryl; wherein  $R^6$ ,  $R^7$ , and  $R^8$  are each independently optionally substituted with from one to six substituents, independently selected from F, Cl, Br, I, nitro, cyano,  $CF_3$ ,  $-NR^9R^{10}$ ,  $-NR^9C(=O)R^{10}$ ,  $-NR^9C(=O)NR^{10}R^{11}$ ,  $-R^9S(=O)_2R^{10}$ ,  $-NR^9S(=O)_2NR^{10}R^{11}$ ,  $-OR^9$ ,  $-OC(=O)R^9$ ,  $-OC(=O)OR^9$ ,  $-OC(=O)NR^9R^{10}$ ,  $-OC(=O)SR^9$ ,  $-C(=O)OR^9$ ,  $-C(=O)R^9$ ,  $-C(=O)NR^6R^7$ ,  $-SR^6$ ,  $-S(=O)R^6$ ,  $-S(=O)_2R^6$ ,  $-S(=O)_2NR^6R^7$ , straight chain or branched  $(C_1-C_8)$ alkyl, straight chain or branched  $(C_2-C_8)$ alkenyl, straight chain or branched  $(C_2-C_8)$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_8)$ cycloalkenyl, 3-8 membered heterocycloalkyl,  $(C_5-C_{11})$ bicycloalkyl,  $(C_7-C_{11})$ bicycloalkenyl, 5-11 membered heterobicycloalkyl, (5-11 membered) heterobicycloalkenyl,  $(C_6-C_{11})$  aryl, 5-12 membered heteroaryl, and  $R^9$ ;

each  $R^9$ ,  $R^{10}$ , and  $R^{11}$  is independently selected from H, straight chain or branched  $(C_1-C_8)$ alkyl, straight chain or branched  $(C_2-C_8)$ alkenyl, straight chain or branched  $(C_2-C_8)$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_8)$ cycloalkenyl, 3-8 membered heterocycloalkyl,  $(C_5-C_{11})$ bicycloalkyl,  $(C_7-C_{11})$ bicycloalkenyl, (5-11 membered heterobicycloalkyl, 5-11 membered heterobicycloalkenyl,  $(C_6-C_{11})$  aryl and 5-12 membered heteroaryl;

with the proviso that when n is one, o is one, m is two, X is oxygen and Y is oxygen or  $NR^1$ , then Q can not be unsubstituted phenyl or phenyl substituted only with one or more substituents selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy,

cyano, hydroxy, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>1</sub>-C<sub>6</sub>) alkoxy, the group -OCH<sub>2</sub>O- attached to both the meta and para positions of the phenyl ring, the group -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- attached to both the meta and para positions of the phenyl ring, and phenoxy or phenyl wherein said phenyl and the phenyl moiety of said phenoxy can optionally be substituted with one or more substituents  
5 selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, (C<sub>1</sub>-C<sub>6</sub>) alkyl, and (C<sub>1</sub>-C<sub>6</sub>) alkoxy;

and all enantiomeric, diastereomeric, and tautomeric isomers of such compounds, and pharmaceutically acceptable salts of such compounds and isomers.

More specific embodiments of this invention relate to compounds of the formula I  
10 wherein X = O and Y = O or NH.

Other more specific embodiments of this invention relate to compounds of the formula I wherein Y = O.

Other more specific embodiments of this invention relate to compounds of the formula I wherein R<sup>1</sup> = methyl.

15 Other more specific embodiments of this invention relate to compounds of the formula I wherein m = 2, o = 1 and n = 1.

Other more specific embodiments of this invention relate to compounds of the formula I wherein Q is (C<sub>6</sub>-C<sub>11</sub>)aryl that is optionally substituted with from one to five substituents independently selected from H, F, Cl, Br, I, nitro, cyano, CF<sub>3</sub>, -NR<sup>3</sup>R<sup>4</sup>, -NR<sup>3</sup>C(=O)R<sup>4</sup>,  
20 -NR<sup>3</sup>C(=O)NR<sup>4</sup>R<sup>5</sup>, -NR<sup>3</sup>S(=O)<sub>2</sub>R<sup>4</sup>, -NR<sup>3</sup>S(=O)<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, -OR<sup>3</sup>, -OR<sup>3</sup>, -OC(=O)OR<sup>3</sup>, -OC(=O)NR<sup>3</sup>R<sup>4</sup>, -OC(=O)SR<sup>3</sup>, -C(=O)OR<sup>3</sup>, -C(=O)R<sup>3</sup>, -C(=O)NR<sup>3</sup>R<sup>4</sup>, -SR<sup>3</sup>, -S(=O)R<sup>3</sup>, -S(=O)<sub>2</sub>R<sup>3</sup>, -S(=O)<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, straight chain or branched (C<sub>1</sub>-C<sub>8</sub>)alkyl, straight chain or branched (C<sub>2</sub>-C<sub>8</sub>)alkenyl, straight chain or branched (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>8</sub>)cycloalkenyl, 3-8 membered heterocycloalkyl, (C<sub>5</sub>-C<sub>11</sub>)bicycloalkyl, (C<sub>7</sub>-C<sub>11</sub>)bicycloalkenyl,  
25 5-11 membered heterobicycloalkyl, 5-11 membered heterobicycloalkenyl, (C<sub>6</sub>-C<sub>11</sub>) aryl, 5-12 membered heteroaryl, and R<sup>3</sup>.

Other more specific embodiments of this invention relate to compounds of the formula I wherein R<sup>3</sup> is (C<sub>6</sub>-C<sub>11</sub>)aryl or (5-12 membered) heteroaryl that is optionally substituted with from one to five substituents independently selected from H, F, Cl, Br, I, nitro, cyano, CF<sub>3</sub>,  
30 -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>C(=O)R<sup>7</sup>, -NR<sup>6</sup>C(=O)NR<sup>7</sup>R<sup>8</sup>, -NR<sup>6</sup>S(=O)<sub>2</sub>R<sup>7</sup>, R<sup>6</sup>S(=O)<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, -OR<sup>6</sup>, -OC(=O)R<sup>6</sup>, -OC(=O)OR<sup>6</sup>, -OC(=O)NR<sup>6</sup>R<sup>7</sup>, -OC(=O)SR<sup>6</sup>, -C(=O)OR<sup>6</sup>, -C(=O)R<sup>6</sup>, -C(=O)NR<sup>6</sup>R<sup>7</sup>, -SR<sup>6</sup>, -S(=O)R<sup>6</sup>, -S(=O)<sub>2</sub>R<sup>6</sup>, -S(=O)<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, straight chain or branched (C<sub>1</sub>-C<sub>8</sub>)alkyl, straight chain or branched (C<sub>2</sub>-C<sub>8</sub>)alkenyl, straight chain or branched (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>8</sub>)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C<sub>5</sub>-C<sub>11</sub>)bicycloalkyl, (C<sub>7</sub>-C<sub>11</sub>)bicycloalkenyl,  
35 C<sub>11</sub>)bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (5-11 membered) heterobicycloalkenyl, (C<sub>6</sub>-C<sub>11</sub>) aryl, (5-12 membered) heteroaryl, and R<sup>6</sup>.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, and t-butyl.

5 The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above. Examples of alkenyl include, but are not limited to, ethenyl and propenyl.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above. Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl.

10 The term "cycloalkyl", as used herein, unless otherwise indicated, includes non-aromatic saturated cyclic alkyl moieties wherein alkyl is as defined above. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. "Bicycloalkyl" groups are non-aromatic saturated carbocyclic groups consisting of two rings. Examples of bicycloalkyl groups include, but are not limited to, bicyclo-[2.2.2]-  
15 octyl and norbornyl. The term "cycloalkenyl" and "bicycloalkenyl" refer to non-aromatic carbocyclic cycloalkyl and bicycloalkyl moieties as defined above, except comprising of one or more carbon-carbon double bonds connecting carbon ring members (an "endocyclic" double bond) and/or one or more carbon-carbon double bonds connecting a carbon ring member and an adjacent non-ring carbon (an "exocyclic" double bond). Examples of cycloalkenyl groups  
20 include, but are not limited to, cyclopentenyl and cyclohexenyl. A non-limiting example of a bicycloalkenyl group is norbornenyl. Cycloalkyl, cycloalkenyl, bicycloalkyl, and bicycloalkenyl groups also include groups similar to those described above for each of these respective categories, but which are substituted with one or more oxo moieties. Examples of such groups with oxo moieties include, but are not limited to oxocyclopentyl, oxocyclobutyl,  
25 oxocyclopentenyl, and norcamphoryl.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen atom. Examples of aryl groups include, but are not limited to phenyl and naphthyl.

30 The terms "heterocyclic" and "heterocycloalkyl", as used herein, refer to non-aromatic cyclic groups containing one or more heteroatoms, preferably from one to four heteroatoms, each selected from O, S and N. "Heterobicycloalkyl" groups are non-aromatic two-ringed cyclic groups, wherein at least one of the rings contains a heteroatom (O, S, or N). The heterocyclic groups of this invention can also include ring systems substituted with one or more oxo moieties. Examples of non-aromatic heterocyclic groups include, but are not limited to,  
35 aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, azepinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, pyrrolinyl, indolinyl,

2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolanyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, quinuclidinyl and quinolizinyl.

The term "heteroaryl", as used herein, refers to aromatic groups containing one or more heteroatoms (O, S, or N). A multicyclic group containing one or more heteroatoms wherein at least one ring of the group is aromatic is a "heteroaryl" group. The heteroaryl groups of this invention can also include ring systems substituted with one or more oxo moieties. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, and azaindolyl.

The foregoing heteroaryl, heterocyclic and heterocycloalkyl groups may be C-attached or N-attached (where such is possible). For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

Examples of specific compounds of this invention are the following compounds of the formula I and their pharmaceutically acceptable salts, hydrates, solvates and optical and other stereoisomers:

- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-bromo-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-pyridin-2-yl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-pyridin-3-yl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-pyridin-4-yl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-nitro-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid naphthalen-2-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carbothioic acid O-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-methoxycarbonyl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 6-bromo-naphthalen-2-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid methyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid isobutyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid pyridin-2-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid pyridin-3-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid octyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-benzyloxy-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-methylsulfanyl-phenyl ester;

- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-indan-1-yl-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-furan-3-yl-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(6-fluoro-pyridin-3-yl)-phenyl  
ester;
- 5 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-benzoyl-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-benzyl-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-imidazol-1-yl-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-benzoyloxy-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-[1,2,4]triazol-1-yl-phenyl ester;
- 10 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(4-acetyl-piperazin-1-yl)-phenyl  
ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-benzooxazol-2-yl-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-benzothiazol-2-yl-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-benzyl-phenyl ester;
- 15 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-benzoyl-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(5-ethoxycarbonyl-pyridin-3-yl)-  
phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4'-nitro-biphenyl-4-yl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2'-nitro-biphenyl-4-yl ester;
- 20 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(6-methyl-pyridin-2-yl)-phenyl  
ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(3,5-dimethyl-isoxazol-4-yl)-  
phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(4-methyl-pyridin-2-yl)-phenyl  
ester;
- 25 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(5-carbamoyl-pyridin-3-yl)-phenyl  
ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(5-cyano-pyridin-3-yl)-phenyl  
ester;
- 30 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3'-nitro-biphenyl-4-yl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-imidazo[1,2-a]pyridin-3-yl-phenyl  
ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-nitro-phenyl ester;  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid ethyl ester;
- 35 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid propyl ester; and  
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-pyridin-3-yl-phenyl ester.



Other examples of specific compounds of this invention are the following compounds of the formula I and their pharmaceutically acceptable salts, hydrates, solvates and optical and other stereoisomers:

- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid (4-bromo-phenyl)amide;
- 5 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-cyano-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-iodo-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2'-methoxy-biphenyl-4-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3'-methoxycarbonyl-biphenyl-4-yl ester;
- 10 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-tert-butyl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-trifluoromethyl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-chloro-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-iodo-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4'-cyano-biphenyl-4-yl ester;
- 15 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4'-bromo-biphenyl-4-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-trifluoromethyl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-fluoro-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-chloro-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-bromo-phenyl ester;
- 20 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-tert-butyl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-iodo-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-phenoxy-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3'-methyl-biphenyl-4-yl ester;
- 25 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4'-chloro-biphenyl-4-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2'-methyl-biphenyl-4-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2'-chloro-biphenyl-4-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3'-chloro-biphenyl-4-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3'-cyano-biphenyl-4-yl ester;
- 30 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4'-methoxy-biphenyl-4-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid biphenyl-3-yl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-bromo-3,5-dimethyl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-bromo-3-methyl-phenyl ester;
- 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-bromo-3-chloro-phenyl ester; and
- 35 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3,4-dimethyl-phenyl ester.

Other examples of specific compounds of this invention are the following compounds of the formula I and their pharmaceutically acceptable salts, hydrates, solvates and optical and other stereoisomers:

- 5           1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2',5'-dimethyl-biphenyl-4-yl ester;  
          1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3',5'-dimethyl-biphenyl-4-yl ester;  
and  
          1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2',3'-dimethyl-biphenyl-4-yl ester.

Another example of a specific compounds of this invention is 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-cyclohexyl-phenyl ester and its pharmaceutically  
10 acceptable salts.

Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the  
15 progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

Compounds of formula I may contain chiral centers and therefore may exist in different enantiomeric and diastereomeric forms. Individual isomers can be obtained by  
20 known methods, such as optical resolution, optically selective reaction, or chromatographic separation in the preparation of the final product or its intermediate. This invention relates to all optical isomers and all stereoisomers of compounds of the formula I, both as racemic mixtures and as individual enantiomers and diastereoisomers of such compounds, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment defined  
25 above that contain or employ them, respectively.

In so far as the compounds of formula I of this invention are basic compounds, they are all capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the base compound from the  
30 reaction mixture as a pharmaceutically unacceptable salt and then simply convert to the free base compound by treatment with an alkaline reagent and thereafter convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent  
35 or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of

10 this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bi-tartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, 5 methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate))salts.

10 The present invention also includes isotopically labelled compounds, which are identical to those recited in formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{11}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the 15 aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labelled compounds of the present invention, for example those into which radioactive isotopes such as  $^3\text{H}$  and  $^{14}\text{C}$  are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e.,  $^3\text{H}$ , and carbon-14, i.e.,  $^{14}\text{C}$ , isotopes are particularly preferred for their ease of preparation and detectability. Further, 20 substitution with heavier isotopes such as deuterium, i.e.,  $^2\text{H}$ , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the reaction schemes and/or in the experimental examples below, by substituting a readily available isotopically 25 labelled reagent for a non-isotopically labelled reagent.

30 The present invention also relates to a pharmaceutical composition for the treatment of schizophrenia in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating schizophrenia and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating schizophrenia in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating schizophrenia.

35 The present invention also relates to a pharmaceutical composition for the treatment of schizophrenia in a mammal, including a human, comprising an  $\alpha 7$  nicotinic receptor agonist compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating schizophrenia in a mammal, including a human, comprising administering to said mammal an  $\alpha 7$  nicotinic receptor agonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

5 The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, tinnitus, hypertension, bulimia, anorexia, obesity, cardiac  
10 arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, multi-infarct dementia, age related cognitive decline, epilepsy,  
15 including petit mal absence epilepsy, HIV induced dementia, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

20 The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS),  
25 cognitive dysfunction, tinnitus, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia,  
30 dyslexia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, HIV induced dementia, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is  
35 effective in treating such disorder or condition.

The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to

- ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, tinnitus, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, HIV induced dementia, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an  $\alpha 7$  nicotinic receptor agonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
- 15       The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS),
- 20       cognitive dysfunction, tinnitus, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia,
- 25       dyslexia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, HIV induced dementia, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an  $\alpha 7$  nicotinic receptor agonizing amount of a compound of the formula I, or a pharmaceutically
- 30       acceptable salt thereof.

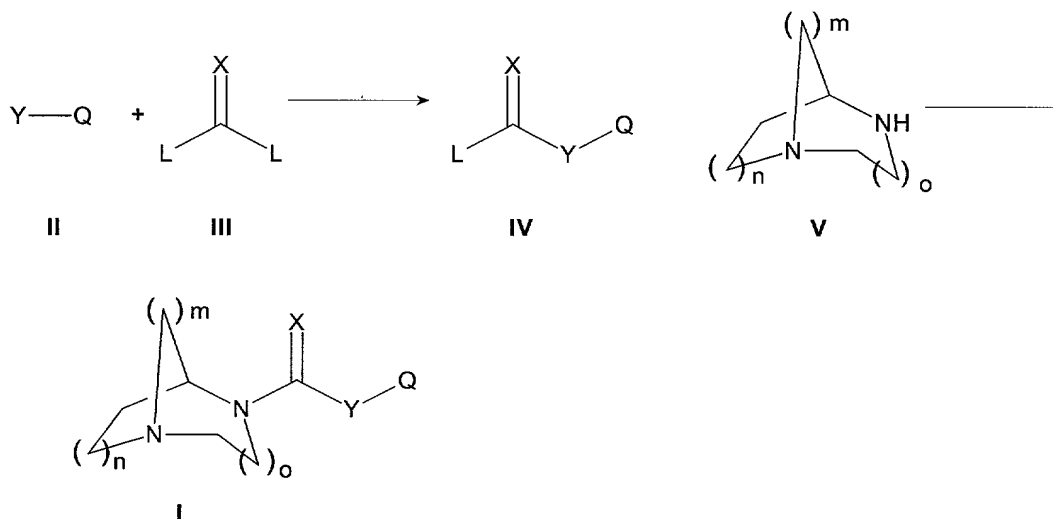
#### DETAILED DESCRIPTION OF THE INVENTION

Compounds of the formula I can be readily prepared according to the methods described below. In the reaction schemes and discussion that follow, m, n, o, X, Y and R<sup>1</sup>, unless otherwise indicated, are defined as they are above in the definition of compounds of the formula I.

As used herein, the expression "reaction inert solvent" refers to a solvent system in which the components do not interact with starting materials, reagents, or intermediates of products in a manner which adversely affects the yield of the desired product.

During any of the following synthetic sequences discussed below it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1999.

Scheme 1



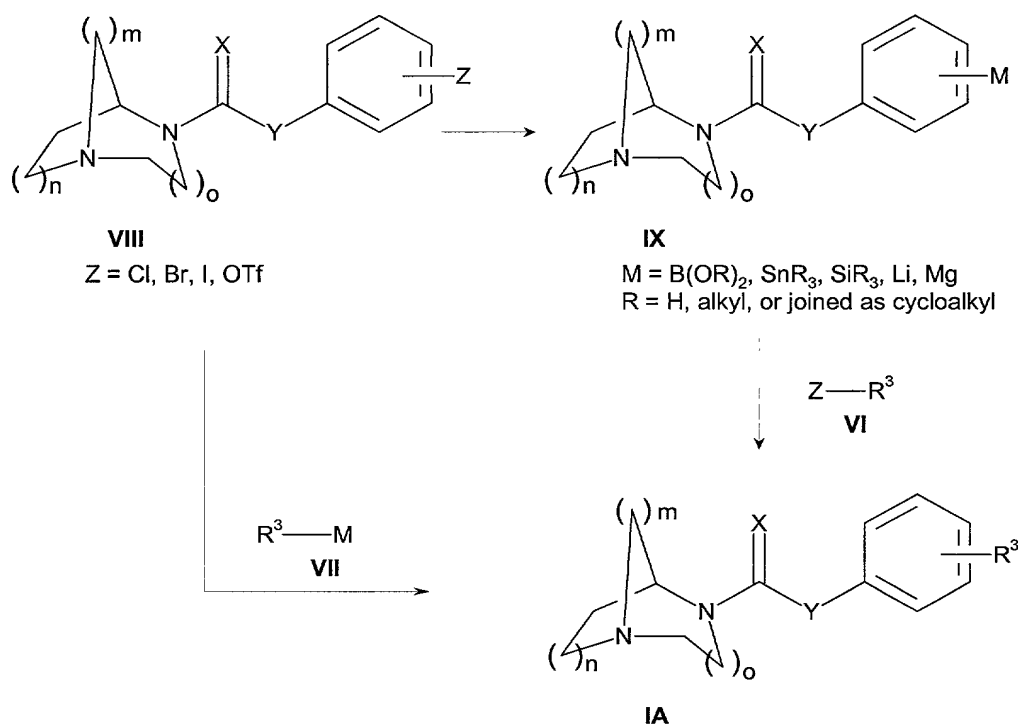
- Compounds of the formula I may be prepared as outlined in Scheme 1. Referring to Scheme I, a compound of the formula II is reacted with a carbonyl donating compound of the formula III, wherein L is a leaving group, for example, chloride, bromide, imidazole, triazole, tetrazole, trichloromethoxy, thiophenol, phenol or substituted phenol (e.g., p-nitrophenol, p-bromophenol, trichloro or trifluoromethyl), preferably chloride, in the presence of a base, for example, triethylamine, diisopropylamine, pyridine, 2,6-lutidine, sodium or potassium hydroxide, sodium or potassium carbonate or bicarbonate, diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, preferably triethylamine. This reaction is typically carried out in a reaction inert solvent such as water, acetonitrile, methylene chloride, chloroform, 1,2-dichloroethane, tetrahydrofuran, diethylether, dioxane, 1,2-dimethoxyethane, benzene, or toluene, preferably toluene, at a temperature from about -50°C to about 110°C, preferably from about 0°C to about 50°C. Upon consumption of the compound of formula II, the resulting compound of formula IV is reacted immediately with additional base such as triethylamine, diisopropylamine, pyridine, 2,6-lutidine or 1,8-diazabicyclo[5.4.0]undec-7-ene or any of the other bases referred to above, preferably triethylamine, in the presence or absence of 4-dimethylaminopyridine or polymer supported 4-dimethylaminopyridine, and with a compound of the formula V at a temperature of from about -10°C to about 110°C, preferably from about 25°C to about 110°C, affording the desired compound of formula I.

- Alternatively, commercially available compounds of formula IV can be reacted with a compound of formula V in the presence of a base such as triethylamine, diisopropylamine, pyridine, 2,6-lutidine or 1,8-diazabicyclo[5.4.0]undec-7-ene or any of the other bases discussed above, with triethylamine being preferred, in the presence or absence of 4-dimethylaminopyridine or polymer supported 4-dimethylaminopyridine, at a temperature from about  $-10^{\circ}\text{C}$  to about  $110^{\circ}\text{C}$ , with from about  $-10^{\circ}\text{C}$  to about  $25^{\circ}\text{C}$  being preferred, affording the desired compound of formula I.
- 5

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Scheme 2



- Scheme 2 illustrates the preparation of compounds of the formula I wherein Q is a (C<sub>6</sub>-C<sub>11</sub>) aryl or (5-12 membered) heteroaryl group, and wherein Q is optionally substituted with a (C<sub>6</sub>-C<sub>11</sub>) aryl or 5-12 membered heteroaryl (R<sup>3</sup>) group. Referring to Scheme 2, treatment of a compound of the formula VIII wherein Z is chloro, bromo, iodo or triflate (OTf) with bis(pinacolato)diboron and a palladium catalyst such as palladium (0) tetrakis(triphenylphosphine), palladium (II) acetate, allyl palladium chloride dimer, tris(dibenzylideneacetone)dipalladium (0), tris(dibenzylideneacetone)dipalladium (0) chloroform adduct, palladium (II) chloride or dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct, preferably dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct, in the presence or absence of a phosphine ligand such as 1,1'-bis(diphenylphosphino)ferrocene, triphenylphosphine, tri-*o*-tolylphosphine, tri-*tert*-butylphosphine, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)-propane, BINAP, 2-biphenyl dicyclohexylphosphine, 2-biphenyl-di-*tert*-butylphosphine, 2-(*N,N*-dimethylamino)-2'-di-*tert*-butylphosphino-biphenyl or 2-(*N,N*-dimethylamino)-2'-dicyclohexylphosphinobiphenyl, preferably 1,1'-bis(diphenylphosphino)ferrocene, and in the presence or absence of a base such as potassium acetate, sodium acetate, cesium acetate, sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate or cesium fluoride, preferably potassium acetate, yields a compound of the formula IX wherein the Z group has been replaced with M,

wherein M = borane pinacol ester. Generally, this reaction is carried out in a reaction inert solvent such as 1,4-dioxane, acetonitrile, methyl sulfoxide, tetrahydrofuran, ethanol, methanol, 2-propanol, toluene, preferably methyl sulfoxide, at a temperature from about 0°C to about 200°C, preferably from about 80°C to about 120°C.

5 Other methods of converting a compound of the formula VIII with the Z group mentioned above into a compound of the formula IX wherein the Z group is replaced with M, wherein M is boronic acid, boronic acid ester or trialkylstannane, are known in the art. For instance, treatment of a compound of the formula VIII, wherein Z is Br or I, with an alkyl lithium reagent such as, but not limited to n-butyl lithium, sec butyl lithium or tert-butyl lithium, 10 in a solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane, hexane, toluene, dioxane or a similar reaction inert solvent, at a temperature from about -100°C to about 25°C affords the corresponding compound of the formula IX wherein Z is Li. Treatment of a solution of this material with a suitable boronic ester such as trimethoxyborane, triethoxyborane or triisopropylborane, followed by a standard aqueous work-up with acid will 15 afford the corresponding compound of the formula IX wherein M is boronic acid.

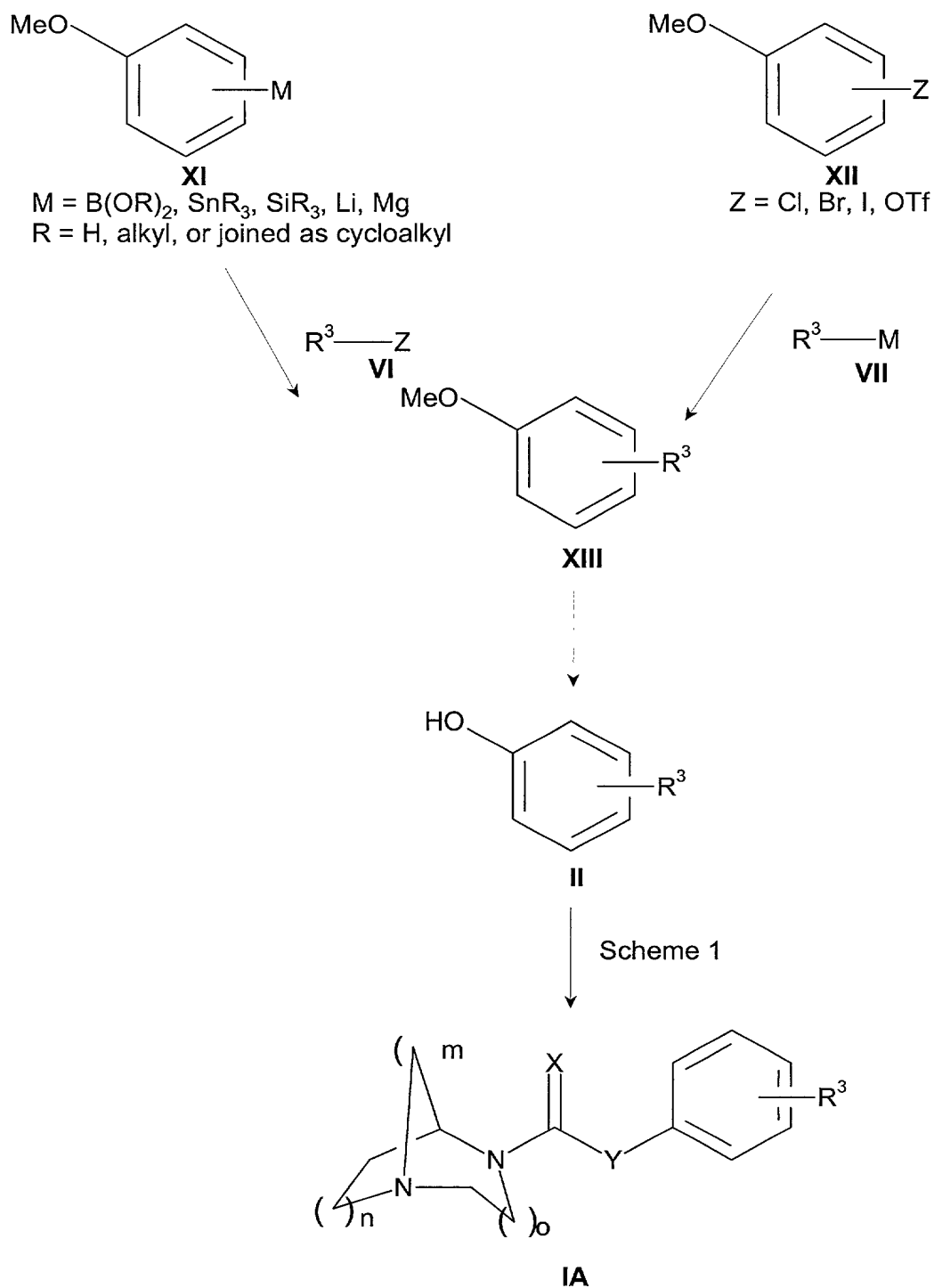
Alternatively, treating a mixture of a compound of the formula VIII wherein Z is Br or I and a boronic ester with an alkyl lithium reagent, as described above, followed by a standard aqueous work-up with acid will afford the corresponding compound of formula IX wherein M is boronic acid. Alternatively, treating a compound of the formula VIII wherein Z is Br or I with 20 an alkyl lithium reagent such as, but not limited to n-butyl lithium, sec butyl lithium or tert-butyl lithium, in a solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane, hexane, toluene, dioxane or a similar reaction inert solvent, at a temperature from about -100°C to about 25°C will afford the corresponding compound of the formula IX wherein M is Li. Treatment of a solution of this material with a suitable trialkylstannyl halide such as, but not limited to 25 trimethylstannyl chloride or bromide or tributylstannyl chloride or bromide, followed by a standard aqueous work-up will afford the corresponding compound of the formula IX wherein M is trimethyl or tributylstannane.

Treatment of a compound of the formula IX wherein M is a boronic acid, boronic ester, or trialkylstannane group, with an aryl or heteroaryl chloride, aryl or heteroaryl bromide, 30 aryl or heteroaryl iodide, or aryl or heteroaryl triflate of the formula VI, preferably an aryl or heteroaryl bromide, with a palladium catalyst such as palladium (0) tetrakis(triphenylphosphine), palladium (II) acetate, allyl palladium chloride dimer, tris(dibenzylideneacetone)dipalladium (0), tris(dibenzylideneacetone)dipalladium (0) chloroform adduct, palladium (II) chloride or dichloro[1,1'- 35 bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct, preferably dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct, in the presence or absence of a phosphine ligand such as 1,1'-bis(diphenylphosphino)ferrocene,

triphenylphosphine, tri-o-tolylphosphine, tri-tert-butylphosphine, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, BINAP, 2-biphenyl dicyclohexylphosphine, 2-biphenyl-di-tert-butylphosphine, 2-(N,N-dimethylamino)-2'-di-tert-butylphosphino-biphenyl or 2-(N,N-dimethylamino)-2'-dicyclohexylphosphinobiphenyl, preferably 1,1'-bis(diphenylphosphino)ferrocene, and in the presence or absence of a base such as potassium phosphate, potassium acetate, sodium acetate, cesium acetate, sodium carbonate, lithium carbonate, potassium carbonate, cesium fluoride or cesium carbonate, preferably potassium phosphate, affords a compound of formula IA. This reaction is typically carried out in a reaction inert solvent such as 1,4-dioxane, acetonitrile, methyl sulfoxide, tetrahydrofuran, ethanol, methanol, 2-propanol, or toluene, preferably 1,4-dioxane, in the presence or absence of from about 1%-about 10% water, preferably about 5% water, at a temperature from about 0°C to about 200°C, preferably from about 60°C to about 100°C.

Alternatively, a compound of the formula VIII can be reacted with a compound of the formula VII, wherein M is a boronic acid, boronic acid ester, borane pinacol ester or trialkylstannane group, using similar reaction conditions as described above, to yield the corresponding compound of formula IA.

Scheme 3



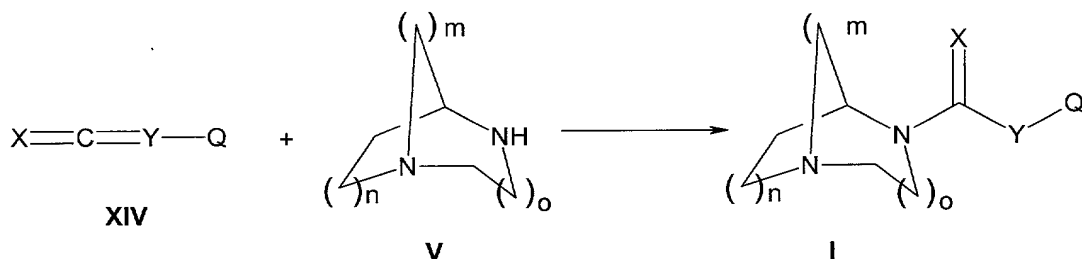
Scheme 3 illustrates an alternative method of preparing compounds of the formula I wherein Q is a (C<sub>6</sub>-C<sub>11</sub>) aryl or (5-12 membered) heteroaryl group, and wherein Q is optionally substituted with a (C<sub>6</sub>-C<sub>11</sub>) aryl or (5-12 membered) heteroaryl (R<sup>3</sup>) group. Referring to

Scheme 3, treatment of a methoxy aryl or heteroaryl ring compound of the formula XI, wherein M = boronic acid, boronic acid ester or a trialkylstannane group, preferably a boronic acid group, with an aryl or heteroaryl chloride, aryl or heteroaryl bromide, aryl or heteroaryl iodide, or aryl or heteroaryl alkoxytriflate of the formula VI wherein Z is defined as above, preferably an aryl or heteroaryl bromide, and with a palladium catalyst such as palladium (0) tetrakis(triphenylphosphine), palladium (II) acetate, allyl palladium chloride dimer, tris(dibenzylideneacetone)dipalladium (0), tris(dibenzylideneacetone)dipalladium (0) chloroform adduct, palladium (II) chloride or dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct, preferably palladium (0) tetrakis(triphenylphosphine), in the presence or absence of a phosphine ligand such as 1,1'-bis(diphenylphosphino)ferrocene, triphenylphosphine, tri-*o*-tolylphosphine, tri-*tert*-butylphosphine, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)-propane, BINAP, 2-biphenyl dicyclohexylphosphine, 2-biphenyl-di-*tert*-butylphosphine, 2-(*N,N*-dimethylamino)-2'-di-*tert*-butylphosphinobiphenyl or 2-(*N,N*-dimethylamino)-2'-dicyclohexylphosphinobiphenyl, and in the presence or absence of a base such as potassium phosphate, potassium acetate, sodium acetate, cesium acetate, sodium carbonate, lithium carbonate, potassium carbonate, cesium fluoride or cesium carbonate, preferably sodium carbonate, affords a compound of the formula XIII. Examples of suitable reaction inert solvents for this reaction are 1,4-dioxane, acetonitrile, methyl sulfoxide, tetrahydrofuran, ethanol, methanol, 2-propanol and toluene, with ethanol being preferred. This reaction can be carried out in the presence or absence of from about 1% to about 10% water, with about 5% water being preferred. The reaction temperature can range from about 0°C to about 200°C, and is preferably from about 60°C to about 100°C.

An alternative method for the preparation of compounds of the formula XIII from a methoxy aryl or heteroaryl ring substituted with a chloride, bromide, iodide or alkoxytriflate group (*i.e.*, a compound of the formula XII) and an aryl or heteroaryl boronic acid, boronic acid ester, or a trialkylstannane group (*i.e.*, a compound of the formula VII) can be performed using a similar procedure to the one described above.

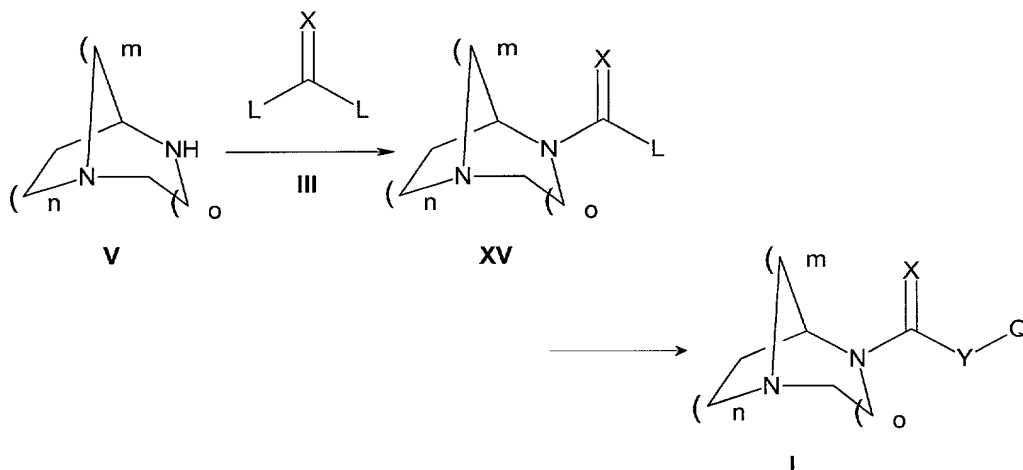
The methoxy group of the compound of formula XIII can be removed, as described in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1999, p250-254, to generate a compound of formula II. The reaction is preferably carried out using hydrobromic acid at a temperature from about room temperature to about 150°C, preferably from about 80°C to about 110°C. Following the chemistry described in Scheme 1, the corresponding compound of formula IA wherein Q is a (C<sub>6</sub>-C<sub>11</sub>) aryl or (5-12 membered) heteroaryl group, and wherein Q is optionally substituted with a (C<sub>6</sub>-C<sub>11</sub>) aryl or (5-12 membered) heteroaryl (R<sup>3</sup>) group can be prepared.

Scheme 4



Scheme 4 illustrates the synthesis of compounds of the formula I wherein Y is N or NH and X is oxygen or sulfur. Referring to Scheme 4, treatment of a compound of formula V with a compound of formula XIV wherein X is oxygen or sulfur and Y is nitrogen in a reaction inert solvent such as acetonitrile, benzene, chloroform, dichloromethane, diethyl ether, dimethylformamide, methyl sulfoxide, ethyl acetate, tetrahydrofuran, or toluene, preferably tetrahydrofuran, at a temperature from about  $-50^{\circ}\text{C}$  to about  $100^{\circ}\text{C}$ , preferably from about  $0^{\circ}\text{C}$  to about  $50^{\circ}\text{C}$ , will provide the corresponding compound of formula I where X is oxygen or sulfur and Y is NH.

Scheme 5



Scheme 5 illustrates a method of preparing compounds of the formula I wherein Y is O or NH and X is oxygen or sulfur. Referring to Scheme 5, treatment of a compound of the formula V with a compound of the formula III, wherein L is a leaving group, for example, chloride, bromide, imidazole, triazole, tetrazole, trichloromethoxy, thiophenol, phenol or substituted phenol (e.g., p-nitrophenol, p-bromophenol, trichloro or trifluoromethyl), preferably chloride, in the presence of a base, for example, triethylamine, diisopropylamine, pyridine, 2,6-lutidine, sodium or potassium hydroxide, sodium or potassium carbonate or bicarbonate, diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene, preferably triethylamine. This reaction is typically carried out in a reaction inert solvent such as water, acetonitrile, methylene chloride, chloroform, 1,2-dichloroethane, tetrahydrofuran, diethylether, dioxane,

1,2-dimethoxyethane, benzene, or toluene, preferably toluene, at a temperature from about -50°C to about 110°C, preferably from about 0°C to about 50°C and affords the corresponding compound of formula XV. Treatment of the resulting compound of formula XV with a suitable phenol or substituted phenol or an aniline or substituted aniline in the presence or absence of  
5 a base such as triethylamine, diisopropylamine, pyridine, 2,6-lutidine or 1,8-diazabicyclo[5.4.0]undec-7-ene or any of the other bases discussed above, with triethylamine being preferred, in a reaction inert solvent such as water, acetonitrile, methylene chloride, chloroform, 1,2-dichloroethane, tetrahydrofuran, diethylether, dioxane, 1,2-dimethoxyethane, benzene, or toluene, preferably toluene at a temperature from about -10°C to about 110°C,  
10 with from about -10°C to about 50°C being preferred, affords the desired compound of formula I.

Isolation and purification of the products is accomplished by standard procedures that are known to a chemist of ordinary skill.

In each of the reactions discussed above, or illustrated in Schemes 1-5 above, pressure  
15 is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, with ambient pressure, i.e., about 1 atmosphere, being preferred as a matter of convenience.

The compounds of the formula I and their pharmaceutically acceptable salts (hereafter "the active compounds") can be administered via either the oral, transdermal (e.g., through the use of a patch), intranasal, sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are preferred. These compounds are, most desirably, administered in dosages ranging from about 0.25 mg up to about 1500 mg per day, preferably from about 0.25 to about 300 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.01 mg to about  
20 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their individual responses to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances,  
25 dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compounds can be administered alone or in combination with  
35 pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated. More particularly, the active compounds can be administered in a wide variety of different dosage forms, e.g., they may be combined with various pharmaceutically acceptable inert carriers in the

form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc can be used for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar, as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration the active ingredient may be combined with various sweetening or flavoring agents, coloring matter and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration, a solution of an active compound in either sesame or peanut oil or in aqueous propylene glycol can be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8), if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

It is also possible to administer the active compounds topically and this can be done by way of creams, a patch, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The effectiveness of the active compounds in suppressing nicotine binding to specific receptor sites can be determined by the following procedure, which is a modification of the methods of Lippiello, P. M. and Fernandes, K. G. (in "The Binding of L-[<sup>3</sup>H]Nicotine To A Single Class of High-Affinity Sites in Rat Brain Membranes", *Molecular Pharm.*, 29, 448-54, (1986)) and Anderson, D. J. and Americ, S. P. (in "Nicotinic Receptor Binding of <sup>3</sup>H-Cystisine, <sup>3</sup>H-Nicotine and <sup>3</sup>H-Methylcarbamylocholine In Rat Brain", *European J. Pharm.*, 253, 261-67 (1994)). Male Sprague-Dawley rats (200-300 g) from Charles River were housed in groups in



hanging stainless steel wire cages and were maintained on a 12 hour light/dark cycle (7 a.m.- 7 p.m. light period). They received standard Purina Rat Chow and water ad libitum. The rats were killed by decapitation. Brains were removed immediately following decapitation. Membranes were prepared from brain tissue according to the methods of Lippiello and Fernandez (Molec. Pharmacol., 29, 448-454, (1986)) with some modifications. Whole brains were removed, rinsed with ice-cold buffer, and homogenized at 0°C in 10 volumes of buffer (w/v) using a Brinkmann Polytron™ (Brinkmann Instruments Inc., Westbury, NY), setting 6, for 30 seconds. The buffer consisted of 50 mM Tris HCl at a pH of 7.5 at room temperature. The homogenate was sedimented by centrifugation (10 minutes; 50,000 x g; 0° to 4°C). The supernatant was poured off and the membranes were gently resuspended with the Polytron and centrifuged again (10 minutes; 50,000 x g; 0°C to 4°C). After the second centrifugation, the membranes were resuspended in assay buffer at a concentration of 1.0g/100mL. The composition of the standard assay buffer was 50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM MgCl<sub>2</sub>, 2 mM CaCl<sub>2</sub> and had a pH of 7.4 at room temperature.

Routine assays were performed in borosilicate glass test tubes. The assay mixture typically consisted of 0.9 mg of membrane protein in a final incubation volume of 1.0 mL. Three sets of tubes were prepared wherein the tubes in each set contained 50µL of vehicle, blank, or test compound solution, respectively. To each tube was added 200µL of [<sup>3</sup>H]-nicotine in assay buffer followed by 750µL of the membrane suspension. The final concentration of nicotine in each tube was 0.9 nM. The final concentration of cytosine in the blank was 1µM. The vehicle consisted of deionized water containing 30µL of 1 N acetic acid per 50 mL of water. The test compounds and cytosine were dissolved in vehicle. Assays were initiated by vortexing after addition of the membrane suspension to the tube. The samples were incubated at 0°C to 4°C in an iced shaking water bath. Incubations were terminated by rapid filtration under vacuum through Whatman GF/B™ glass fiber filters (Brandel Biomedical Research & Development Laboratories, Inc., Gaithersburg, MD) using a Brandel™ multi-manifold tissue harvester (Brandel Biomedical Research & Development Laboratories, Inc., Gaithersburg, MD). Following the initial filtration of the assay mixture, filters were washed two times with ice-cold assay buffer (5 ml each). The filters were then placed in counting vials and mixed vigorously with 20 ml of Ready Safe™ (Beckman, Fullerton, CA) before quantification of radioactivity. Samples were counted in a LKB Wallac Rackbeta™ liquid scintillation counter (Wallac Inc., Gaithersburg, MD) at 40-50% efficiency. All determinations were in triplicate.

Calculations: Specific binding (C) to the membrane is the difference between total binding in the samples containing vehicle only and membrane (A) and non-specific binding in the samples containing the membrane and cytosine (B), i.e.,

$$\text{Specific binding} = (C) = (A) - (B).$$

Specific binding in the presence of the test compound (E) is the difference between the total binding in the presence of the test compound (D) and non-specific binding (B), i.e.,  $(E) = (D) - (B)$ .

$\% \text{ Inhibition} = (1 - ((E)/(C))) \text{ times } 100.$

- 5        The compounds of the invention that were tested in the above assay exhibited  $IC_{50}$  values of less than  $10\mu M$ .

10         $[^{125}I]$ -Bungarotoxin binding to nicotinic receptors in  $GH_4Cl$  cells: Membrane preparations were made for nicotinic receptors expressed in  $GH_4Cl$  cell line. Briefly, one gram of cells by wet weight were homogenized with a polytron in 25 mls of buffer containing  
15        20 mM Hepes, 118 mM NaCl, 4.5 mM KCl, 2.5 mM  $CaCl_2$ , 1.2 mM  $MgSO_4$ , pH 7.5. The homogenate was centrifuged at  $40,000 \times g$  for 10 min at  $4^\circ C$ , the resulting pellet was homogenized and centrifuged again as described above. The final pellet was resuspended in 20 mls of the same buffer. Radioligand binding was carried out with  $[^{125}I]$  alpha-bungarotoxin from New England Nuclear, specific activity about  $16 \mu Ci/ug$ , used at 0.4 nM final  
20        concentration in a 96 well microtiter plate. The plates were incubated at  $37^\circ C$  for 2 hours with 25  $\mu l$  drugs or vehicle for total binding, 100  $\mu l$   $[^{125}I]$  Bungarotoxin and 125  $\mu l$  tissue preparation. Nonspecific binding was determined in the presence of methyllycaconitine at 1  $\mu M$  final concentration. The reaction was terminated by filtration using 0.5% Polyethylene imine treated Whatman GF/B<sup>TM</sup> glass fiberfilters (Brandel Biomedical Research &  
25        Development Laboratories, Inc., Gaithersburg, MD) on a Skatron cell harvester (Molecular Devices Corporation, Sunnyvale, CA) with ice-cold buffer, filters were dried overnight, and counted on a Beta plate counter using Betaplate Scint. (Wallac Inc., Gaithersburg, MD). Data are expressed as  $IC_{50}$ 's (concentration that inhibits 50% of the specific binding) or as an apparent  $K_i$ ,  $IC_{50}/(1 + [L]/K_D)$ .  $[L]$  = ligand concentration,  $K_D$  = affinity constant for  $[^{125}I]$  ligand determined in separate experiment.

30         $[^{125}I]$ -Bungarotoxin binding to alpha1 nicotinic receptors in Torpedo electroplax membranes: Frozen Torpedo electroplax membranes (100  $\mu l$ ) were resuspended in 213 mls of buffer containing 20 mM Hepes, 118 mM NaCl, 4.5 mM KCl, 2.5 mM  $CaCl_2$ , 1.2 mM  $MgSO_4$ , pH 7.5 with 2 mg/ml BSA. Radioligand binding was carried out with  $[^{125}I]$  alpha-bungarotoxin from New England Nuclear, specific activity about  $16\mu Ci/\mu g$ , used at 0.4 nM final concentration in a 96 well microtiter plate. The plates were incubated at  $37^\circ C$  for 3  
35        hours with 25  $\mu l$  drugs or vehicle for total binding, 100  $\mu l$   $[^{125}I]$  Bungarotoxin and 125  $\mu l$  tissue preparation. Nonspecific binding was determined in the presence of alpha-bungarotoxin at 1  $\mu M$  final concentration. The reaction was terminated by filtration using 0.5% Polyethylene imine treated GF/B filters on a Brandel cell harvester with ice-cold buffer, filters were dried overnight, and counted on a Beta plate counter using Betaplate Scint. Data are expressed as  $IC_{50}$ 's (concentration that inhibits 50% of the specific binding) or as an apparent  $K_i$ ,

IC50/1+[L]/KD. [L] = ligand concentration, KD = affinity constant for [<sup>125</sup>I] ligand determined in separate experiment.

5-HT<sub>3</sub> Receptor Binding in NG-108 Cells Using 3H-LY278584: NG-108 cells endogenously express 5-HT<sub>3</sub> receptors. Cells are grown in DMEM containing 10% fetal bovine serum supplemented with L-glutamine (1:100). Cells are grown to confluence and harvested by removing the media, rinsing the flasks with phosphate buffered saline (PBS) and then allowed to sit for a 2-3 minutes with PBS containing 5 mM EDTA. Cells are dislodged and poured into a centrifuge tube. Flasks are rinsed with PBS and added to centrifuge tube. The cells are centrifuged for ten minutes at 40,000 x g (20,000 rpm in Sorvall SS34 rotor(Kendro Laboratory Products, Newtown, CT)). The supernatant is discarded (into chlorox) and at this point the remaining pellet is weighed and can be stored frozen (-80 degrees C) until used in the binding assay. Pellets (fresh or frozen - 250 mgs per 96 well plate) are homogenized in 50 mM Tris HCl buffer containing 2 mM MgCl<sub>2</sub> (pH 7.4) using a Polytron homogenizer (setting 15,000 rpm) for ten seconds. The homogenate is centrifuged for ten minutes at 40,000 x g. The supernatant is discarded and the pellet resuspended with the Polytron in fresh ice-cold 50 mM Tris HCl containing 2 mM MgCl<sub>2</sub> (pH 7.4) buffer and centrifuged again. The final pellet is resuspended in assay buffer (50 mM Tris HCl buffer (pH 7.4 at 37°C degrees) containing 154 mM NaCl,) for a final tissue concentration of 12.5 mg per mL buffer (1.25 X final concentration). Incubations were initiated by the addition of tissue homogenate to 96 well polypropylene plates containing test compounds that have been diluted in 10% DMSO/50 mM Tris buffer and radioligand (1 nM final concentration of 3H-LY278584). Nonspecific binding was determined using a saturating concentration of a known potent 5-HT<sub>3</sub> antagonist (10 uM ICS-205930). After an hour incubation at 37°C in a water bath, the incubation is ended by rapid filtration under vacuum through a fire-treated Whatman GF/B glass fiber filter (presoaked in 0.5% Polyethylene imine for two hours and dried) using a 96 well Skatron Harvester (3 sec pre-wet; 20 seconds wash; 15 seconds dry). Filters are dried overnight and then placed into Wallac sample bags with 10 mLs BetaScint. Radioactivity is quantified by liquid scintillation counting using a BetaPlate counter (Wallac, Gaithersburg, MD). The percent inhibition of specific binding is calculated for each concentration of test compound. An IC50 value (the concentration which inhibits 50% of the specific binding) is determined by linear regression of the concentration-response data (log concentration vs. logit percent values). Ki values are calculated according to Cheng & Prusoff -  $K_i = IC_{50}/(1 + (L/K_d))$ , where L is the concentration of the radioligand used in the experiment and the Kd value is the dissociation constant for the radioligand determined in separate saturation experiments.

The following experimental examples illustrate but do not limit the present invention. In the examples, commercial reagents were used without further purification. Purification by

chromatography was done on prepacked silica columns from Biotage (Dyax Corp, Biotage Division, Charlottesville, VA). Melting points (mp) were obtained using a Mettler Toledo FP62 melting point apparatus (Mettler-Toledo, Inc., Worthington, OH) with a temperature ramp rate of 10°C/min and are uncorrected. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded in deuterated solvents on a Varian INOVA400 (400 MHz) spectrometer (Varian NMR Systems, Palo Alto, CA). Chemical shifts are reported in parts per million (ppm, δ) relative to Me<sub>4</sub>Si (δ 0.00). Proton NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sep), multiplet (m) apparent (ap) and broad (br). Coupling constants are reported in hertz (Hz). Carbon-13 nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded on a Varian INOVA400 (100 MHz). Chemical shifts are reported in ppm (δ) relative to the central line of the 1:1:1 triplet of deuteriochloroform (δ 77.00), the center line of deuteromethanol (δ 49.0) or deuterodimethylsulfoxide (δ 39.7). The number of carbon resonance's reported may not match the actual number of carbons in some molecules due to magnetically and chemically equivalent carbons and may exceed the number of actual carbons due to conformational isomers. Mass spectra (MS) were obtained using a Waters ZMD mass spectrometer using flow injection atmospheric pressure chemical ionization (APCI) (Waters Corporation, Milford, Mass). Gas chromatography with mass detection (GCMS) were obtained using a Hewlett Packard HP 6890 series GC system with a HP 5973 mass selective detector and a HP-1 (crosslinked methyl siloxane) column (Agilent Technologies, Wilmington, DE). Room temperature (RT) refers to 20-25 °C. The abbreviations "h" and "hrs" refer to "hours". 1,4-Diaza-bicyclo[3.2.2]nonane was prepared via slight modifications of the published procedure: see, Rubstov, M.V.; Mikhлина, E.E.; Vorob'eva, V. Ya.; Yanina, A. Zh. Obshch. Khim. 1964, V34, 2222-2226.

#### Example 1

##### 1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID PHENYL ESTER

Phenyl chloroformate (0.219 mL, 1.75 mmol) was added dropwise to a mixture of 1,4-diaza-bicyclo[3.2.2]nonane (200 mg, 1.6 mmol), 4-dimethylaminopyridine (194 mg, 1.6 mmol), pyridine (0.26 mL, 3.17 mmol) and methylene chloride (5.3 mL, 0.3 M) at -10°C (ice/acetone bath). The bath was removed and the mixture was allowed to stir at RT for 15 hrs until the reaction was complete as determined by GCMS. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (~5 mL) and treated with an excess of NaHCO<sub>3</sub> saturated solution (~5 mL). The layers were partitioned and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic extracts were washed successively with H<sub>2</sub>O (10 mL) then brine (10 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the crude residue was purified by chromatography (Biotage 40M column) eluting with 5% MeOH in CHCl<sub>3</sub> containing 20 drops

of NH<sub>4</sub>OH per liter of eluent to afford 145 mg (37% yield) of the title compound as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.35 (t, 2H, J = 7.7 Hz), 7.20-7.16 (m, 1H), 7.12-7.09 (m, 2H), 4.45-4.43 (m, 1H, major), 4.37-4.36 (m, minor), 3.81 (t, J = 5.8 Hz, minor), 3.74 (t, 2H, J = 5.8 Hz, major), 3.16-2.97 (m, 6H), 2.13-2.02 (m, 2H), 1.78-1.67 (m, 2H); <sup>13</sup>C (CDCl<sub>3</sub>, 100 MHz) δ 154.2, 153.4, 151.7, 151.6, 129.51, 129.47, 125.5, 125.4, 122.0, 57.6, 57.3, 49.1, 49.0, 46.54, 46.48, 43.3, 43.0, 27.5, 26.8; MS (CI) m/z 247.3 (M + H). The hydrochloride salt was prepared by dissolving the title compound in iPrOH and adding 0.1 mL of 6 M hydrochloric acid; m.p = 254.8°C.

Unless otherwise indicated, the procedures analogous to the procedure described in Example 1 were used to prepare the title compounds of Examples 2 through 17.

#### Example 2

##### 1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-BROMO-PHENYL ESTER

4-Bromophenyl chloroformate was used. The title compound was prepared in 67% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.44 (d, 2H, J = 8.7 Hz), 7.01-6.97 (m, 2H), 4.40-4.39 (m, 1H, major), 4.34-4.33 (m, minor), 3.78 (t, J = 5.8 Hz, minor), 3.71 (t, 2H, J = 5.8 Hz, major), 3.15-2.95 (m, 6H), 2.09-2.00 (m, 2H), 1.77-1.66 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 153.7, 152.9, 150.8, 150.7, 132.5, 132.4, 123.8, 118.4, 118.3, 57.5, 57.2, 49.2, 49.1, 46.5, 46.4, 43.4, 43.1, 27.6, 26.8; MS (CI) m/z 327.1 (M + H), 325.1. The hydrochloride salt was prepared; m.p. = 249.1°C.

#### Example 3

##### 1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-METHOXY-PHENYL ESTER

4-Methoxyphenyl chloroformate was used. The title compound was prepared in 40% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.03-6.99 (m, 2H), 6.89-6.84 (m, 2H), 4.49-4.47 (m, 1H, major), 4.42-4.41 (m, minor), 3.86 (t, J = 5.8 Hz, minor), 3.79-3.76 (m, 5H), 3.24-3.05 (m, 6H), 2.16-2.06 (m, 2H), 1.84-1.74 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 157.2, 154.5, 153.7, 145.1, 145.0, 122.7, 114.6, 114.5, 57.3, 57.1, 55.8, 48.6, 46.5, 46.4, 42.4, 42.2, 26.9, 26.1; MS (CI) m/z 277.3 (M + H), 245.4. The hydrochloride salt was prepared; m.p. = 269.7°C.

#### Example 4

##### 1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-FLUORO-PHENYL ESTER

4-Fluorophenyl chloroformate was used. The title compound was prepared in 31% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.08-6.97 (m, 4H), 4.43-4.42 (m, 1H, major), 4.36-4.34 (m, minor), 3.80 (t, J = 5.8 Hz, minor), 3.73 (t, 2H, J = 5.8 Hz, major), 3.16-2.98 (m, 6H), 2.10-1.98 (m, 2H), 1.78-1.67 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 161.4, 161.3, 158.9, 158.9, 147.5, 147.4, 123.4, 123.3, 116.2, 116.1, 116.0, 115.9, 57.6, 57.2, 49.2, 49.0, 46.5, 46.4, 43.3, 43.0, 27.5, 26.8; MS (CI) m/z 265 (M + H), 245. The hydrochloride salt was prepared; m.p. = 276.8°C.

Example 5

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-NITRO-PHENYL ESTER

4-Nitrophenyl chloroformate was used. The title compound was prepared in 40% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  8.22 (d, 2H, J = 8.7 Hz), 7.30-7.26 (m, 2H), 4.43-4.42 (m, 1H, major), 4.36-4.35 (m, minor), 3.81 (t, J = 5.8 Hz, minor), 3.74 (t, 2H, J = 5.8 Hz, major), 3.17-2.98 (m, 6H), 2.09-2.02 (m, 2H), 1.81-1.69 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  156.6, 156.5, 152.8, 152.0, 145.0, 144.9, 125.30, 125.27, 122.54, 122.49, 57.4, 57.1, 49.5, 49.4, 46.5, 46.4, 43.6, 43.2, 27.5, 26.7; MS (CI) m/z 292 (M + H), 245. The hydrochloride salt was prepared; m.p. = 267.5°C.

Example 6

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2-NITRO-PHENYL ESTER

2-Nitrophenyl chloroformate was used. The title compound was prepared in 41% yield as an oily yellow solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  8.06 (td, 1H, J = 8.5, 1.7 Hz), 7.65-7.60 (m, 1H), 7.36-7.26 (m, 2H), 4.47-4.46 (m, minor), 4.30-4.29 (m, 1H, major), 3.84 (t, 2H, J = 5.8 Hz, major), 3.73 (t, J = 5.8 Hz, minor), 3.16-3.03 (m, 6H), 2.19-2.06 (m, 2H), 1.77-1.67 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  152.6, 152.0, 145.4, 145.2, 134.9, 134.8, 126.2, 126.0, 125.9, 125.6, 57.3, 57.2, 49.7, 49.5, 46.5, 43.7, 43.4, 27.4, 26.6; MS (CI) m/z 292 (M + H), 245. The hydrochloride salt was prepared; m.p. = 260.4°C.

Example 7

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID NAPHTHALEN-2-YL ESTER

2-Naphthyl chloroformate was used. The title compound was prepared in 31% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.85-7.68 (m, 3H), 7.58 (d, 1H, J = 6.2 Hz), 7.48-7.41 (m, 2H), 7.30-7.26 (m, 1H), 4.51-4.49 (m, 1H, major), 4.41-4.39 (m, minor), 3.86 (t, J = 5.8 Hz, minor), 3.77 (t, 2H, J = 5.8 Hz, major), 3.17-2.99 (m, 6H), 2.15-2.05 (m, 2H), 1.78-1.68 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  154.3, 153.5, 149.4, 149.3, 134.1, 131.44, 131.39, 129.5, 129.4, 128.0, 127.8, 126.7, 126.6, 125.7, 125.6, 121.9, 121.8, 118.72, 118.68, 57.6, 57.3, 49.2, 49.1, 46.6, 46.5, 43.4, 43.1, 27.6, 26.8; MS (CI) m/z 297 (M + H). The hydrochloride salt was prepared; m.p. = 255.5°C.

Example 8

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-CHLORO-PHENYL ESTER

4-Chlorophenyl chloroformate was used. The title compound was prepared in 49% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.28 (d, 2H, J = 8.7 Hz), 7.05-7.02 (m, 2H), 4.40-4.39 (m, 1H, major), 4.33-4.32 (m, minor), 3.78 (t, J = 5.8 Hz, minor), 3.71 (t, 2H, J = 5.8 Hz, major), 3.14-2.95 (m, 6H), 2.06-2.01 (m, 2H), 1.76-1.65 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.8, 153.0, 150.2, 150.1, 130.7, 130.6, 129.5,

129.4, 123.4, 57.5, 57.2, 49.2, 49.1, 46.5, 46.4, 43.4, 43.1, 27.6, 26.8; MS (CI) m/z 281 (M + H), 245. The hydrochloride salt was prepared; m.p. = 257.5°C.

Example 9

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID P-TOLYL ESTER

5 p-Tolyl chloroformate was used. The title compound was prepared in 15% yield as a clear oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.14 (d, 2H, J = 8.3 Hz), 7.00-6.97 (m, 2H), 4.44-4.43 (m, 1H, major), 4.37-4.35 (m, minor), 3.82 (t, J = 5.8 Hz, minor), 3.74 (t, 2H, J = 5.8 Hz, major), 3.16-2.97 (m, 6H), 2.33 (s, 3H), 2.12-2.02 (m, 2H), 1.78-1.68 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 154.5, 149.5, 149.4, 135.0, 134.9, 130.02, 10  
129.97, 121.68, 57.7, 57.4, 49.1, 49.0, 46.6, 46.5, 43.4, 43.1, 27.6, 27.0, 21.1; MS (CI) m/z 261.2 (M + H). The hydrochloride salt was prepared; m.p. = 275.7°C.

Example 10

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOTHIOIC ACID O-PHENYL ESTER

Phenyl chlorothione carbonate was used. The title compound was prepared in 58%  
15 yield as a brown oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.40 (t, 2H, J = 7.9 Hz), 7.28-7.24 (m, 1H), 7.06 (dd, 2H, J = 8.5, 1.0 Hz), 5.11-5.07 (m, minor), 4.89-4.86 (m, 1H, major), 4.40 (t, 2H, J = 5.8 Hz, major), 4.13 (t, J = 5.8 Hz, minor), 3.19-2.98 (m, 6H), 2.33-2.16 (m, 2H), 1.83-1.72 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 154.3, 142.6, 129.44, 129.41, 126.2, 126.1, 123.1, 122.9, 56.8, 56.0, 54.9, 51.6, 49.6, 46.6, 46.4, 45.3,  
20 27.2, 26.0; MS (CI) m/z 263.3 (M + H). The hydrochloride salt was prepared; m.p. = 272.2°C.

Example 11

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID BENZYL ESTER

Benzyl chloroformate was used. The title compound was prepared in 15% yield to give an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.35-7.25 (m, 25  
5H), 5.13 (d, 2H, J = 7.9 Hz), 4.33-4.32 (m, minor), 4.25-4.24 (m, 1H, major), 3.70-3.64 (m, 2H), 3.10-2.91 (m, 6H), 2.10-1.90 (m, 2H), 1.71-1.60 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 155.0, 137.1, 128.7, 128.2, 128.1, 128.0, 67.3, 67.2, 57.7, 57.5, 48.7, 48.4, 46.6, 46.5, 42.8, 27.6, 27.0; MS (CI) m/z 261.3 (M + H). The hydrochloride salt was prepared; m.p. = 235.6°C.

Example 12

30 1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-METHOXYCARBONYL-PHENYL ESTER

6-Methoxycarbonyl benzyl chloroformate was used. The title compound was prepared in 25% yield to give a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 8.02 (d, 2H, J = 8.7 Hz), 7.19-7.16 (m, 2H), 4.42-4.39 (m, 1H, major), 4.35-4.32 (m, minor), 3.87 (s, 3H), 3.79 (t, J = 5.8 Hz, minor), 3.72 (t, 2H, J = 5.8 Hz, major), 3.14-2.94 (m, 6H), 2.09-2.00 (m, 2H), 1.77-1.67 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 166.7, 166.6, 155.44, 155.37, 153.4, 152.6, 131.24, 131.20, 127.2, 127.1, 121.83, 121.78,  
35

57.6, 57.2, 52.4, 49.3, 49.2, 46.5, 46.4, 43.6, 43.2, 27.6, 26.9; MS (CI) m/z 305.3 (M + H). The hydrochloride salt was prepared; m.p. = 237.4°C.

Example 13

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID METHYL ESTER

5 Methyl chloroformate was used and 4-dimethylaminopyridine was not added to the reaction mixture. The title compound was prepared in 42% yield as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 4.29-4.28 (m, minor), 4.17-4.15 (m, 1H, major), 3.68 (s, 3H, major), 3.67 (s, minor), 3.65 (t, 2H, J = 5.8 Hz, major), 3.61 (t, J = 5.8 Hz, minor), 3.09-2.89 (m, 6H), 1.95-1.92 (m, 2H), 1.69-1.59 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100  
10 MHz) δ 154.5, 57.6, 57.4, 52.9, 52.6, 48.5, 48.2, 46.54, 46.49, 42.7, 27.4, 26.9; MS (CI) m/z 185.3 (M + H). The hydrochloride salt was prepared; m.p. = 198.7°C.

Example 14

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID ISOBUTYL ESTER

15 Isobutyl chloroformate was used and 4-dimethylaminopyridine was not added to the reaction mixture. The title compound was prepared in 58% yield as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 4.32-4.30 (m, minor), 4.22-4.20 (m, 1H, major), 3.87-3.84 (m, 2H), 3.69-3.62 (m, 2H), 3.12-2.92 (m, 6H), 1.98-1.91 (m, 3H), 1.70-1.62 (m, 2H), 0.92 (d, 6H, J = 6.6 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 156.5, 71.8, 71.6, 57.6, 57.5, 48.3, 48.2, 46.6, 46.5, 42.4, 28.3, 27.4, 26.9, 19.4, 19.2; GCMS m/z 226 (M). The  
20 hydrochloride salt was prepared; m.p. = 266.5 °C.

Example 15

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID OCTYL ESTER

Octyl chloroformate was used and 4-dimethylaminopyridine was not added to the reaction mixture. The title compound was prepared in 74% yield as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 4.35-4.33 (m, minor), 4.23-4.21 (m, 1H, major), 4.13-4.04 (m, 2H), 3.72-3.61 (m, 2H), 3.15-2.95 (m, 6H), 2.03-1.96 (m, 2H), 1.70-1.52 (m, 4H), 1.40-1.20 (m, 10H), 0.89-0.85 (m, 3H); MS (CI) m/z 283.3 (M + H). The  
25 hydrochloride salt was prepared; m.p. = 217.5°C.

Example 16

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID ETHYL ESTER

30 Ethyl chloroformate was used and polymer supported DMAP was used in place of DMAP, Et<sub>3</sub>N was used in place of pyridine, and toluene was used in place of CH<sub>2</sub>Cl<sub>2</sub>. The title compound was prepared in 22% yield as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 4.31-4.29 (m, minor), 4.20-4.18 (m, 1H, major), 4.15-4.07 (m, 2H), 3.67-3.59 (m, 2H), 3.10-2.90 (m, 6H), 2.00-1.90 (m, 2H), 1.71-1.62 (m, 2H), 1.23 (t, 3H, J = 7.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 155.2, 61.5, 61.4, 57.5, 48.2, 48.1, 46.5, 42.3, 27.3, 26.8, 15.0; MS (CI) m/z 199.2 (M + H). The hydrochloride salt was prepared; m.p. = 207.7°C.



Example 17

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID PROPYL ESTER

Propyl chloroformate was used and polymer supported DMAP was used in place of DMAP, Et<sub>3</sub>N was used in place of pyridine, and toluene was used in place of CH<sub>2</sub>Cl<sub>2</sub>. The title compound was prepared in 36% yield as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 4.29-4.27 (m, minor), 4.19-4.17 (m, 1H, major), 4.01 (m, 2H), 3.66-3.59 (m, 2H), 3.08-2.87 (m, 6H), 1.98-1.89 (m, 2H), 1.68-1.59 (m, 4H), 0.92 (t, 3H, J = 7.2 Hz); MS (CI) m/z 213.3 (M + H). The hydrochloride salt was prepared; m.p. = 242.0°C.

Example 18

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 6-BROMO-NAPHTHALEN-2-YL ESTER

A solution of triphosgene (188 mg, 0.634 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was slowly added to a solution of 6-bromo-2-naphthol (389 mg, 1.75 mmol) and pyridine (167 μL, 2.06 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) at RT. A white precipitate formed and after a period of 35 min. additional pyridine (257 μL, 3.17 mmol) was added and the reaction flask was placed in an ice/water bath. Next a solution of 1,4-diaza-bicyclo[3.2.2]nonane (200 mg, 1.59 mmol) and dimethylaminopyridine (194 mg, 1.59 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was added. The bath was removed and the mixture was allowed to warm to RT. After a period of 30 min at RT a saturated solution of NaHCO<sub>3</sub> (5 mL) was added. The layers were partitioned and the aqueous layer was extracted with CHCl<sub>3</sub> (3 x 5 mL). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The crude residue was purified by chromatography (Biotage 40M column) eluting with 5% MeOH in CHCl<sub>3</sub> containing 20 drops of NH<sub>4</sub>OH per liter of eluent to afford 39 mg (7% yield) of the title compound as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.98 (s, 1H), 7.75 (d, 1H, J = 9.1 Hz), 7.65 (d, 1H, J = 8.7 Hz), 7.56-7.52 (m, 2H), 7.32-7.28 (m, 1H), 4.52-4.50 (m, 1H, major), 4.42-4.40 (m, minor), 3.88 (t, J = 5.8 Hz, minor), 3.78 (t, 2H, J = 5.8 Hz, major), 3.21-3.03 (m, 6H), 2.18-2.06 (m, 2H), 1.84-1.72 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 154.1, 153.3, 149.6, 149.5, 132.5, 132.44, 132.39, 130.1, 130.03, 130.0, 129.4, 128.6, 128.5, 123.0, 122.9, 119.52, 119.48, 118.81, 118.76, 57.5, 57.2, 49.14, 49.09, 46.54, 46.47, 43.3, 42.9, 27.5, 26.7; MS (CI) m/z 377.1 (M + H), 375.1. The hydrochloride salt was prepared by dissolving the title compound in EtOH and adding 0.1 mL of 6 M hydrochloric acid; m.p = 174.2°C.

The procedure described in Example 18 was used to prepare the title compound of Example 19.

Example 19

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID PYRIDIN-3-YL ESTER

3-Hydroxypyridine was used. The title compound was prepared in 12% yield as an oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  8.43 (ap t, 2H,  $J = 2.9$  Hz), 7.53-7.49 (m, 1H), 7.32-7.28 (m, 1H), 4.46-4.44 (m, 1H, major), 4.37-4.35 (m, minor), 3.83 (t,  $J = 5.8$  Hz, minor), 3.75 (t, 2H,  $J = 5.8$  Hz, major), 3.18-2.98 (m, 6H), 2.13-2.02 (m, 2H), 1.81-1.69 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.4, 152.7, 148.3, 148.2, 146.6, 146.5, 143.8, 129.6, 123.93, 123.89, 57.5, 57.2, 49.4, 49.2, 46.5, 46.4, 43.5, 43.2, 27.5, 26.8; MS (CI)  $m/z$  248.3 ( $M + H$ ). The dihydrochloride salt was prepared; m.p. = 164.7°C.

Example 20

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID PYRIDIN-2-YL ESTER

A solution of triphosgene (240 mg, 0.80 mmol) in  $\text{ClCH}_2\text{CH}_2\text{Cl}$  (5.0 mL) was slowly added to a solution of 2-hydroxypyridine (210 mg, 2.2 mmol) and  $\text{Et}_3\text{N}$  (280  $\mu\text{L}$ , 4.0 mmol) in  $\text{ClCH}_2\text{CH}_2\text{Cl}$  (15.0 mL) at RT. The mixture was stirred for a period of 2 h. then cooled to -10 °C (ice/acetone).  $\text{Et}_3\text{N}$  (280  $\mu\text{L}$ , 4.0 mmol), polymer supported DMAP (140 mg, 0.2 mmol) and 1,4-diaza-bicyclo[3.2.2]nonane (256 mg, 2.0 mmol) were added. The bath was removed after a period of 30 min. and the mixture was allowed to warm to RT. The reaction mixture was filtered and concentrated. The crude residue was purified by chromatography (Biotage 40M column) eluting with 5% MeOH in  $\text{CHCl}_3$  containing 20 drops of  $\text{NH}_4\text{OH}$  per liter of eluent to afford 188 mg (38% yield) of the title compound as an oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  8.09 (dd, 1H,  $J = 5.0, 1.7$  Hz), 7.61 (td, 1H,  $J = 8.3, 1.6$  Hz), 7.04-7.01 (m, 1H), 6.90 (dd, 1H,  $J = 8.3, 4.2$  Hz), 4.28-4.27 (m, 1H, major), 4.14-4.12 (m, minor), 3.66 (t,  $J = 5.8$  Hz, minor), 3.54 (t, 2H,  $J = 5.8$  Hz, major), 2.92-2.78 (m, 6H), 1.98-1.84 (m, 2H), 1.64-1.52 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  158.3, 158.1, 153.2, 152.5, 147.84, 147.80, 140.1, 121.9, 116.7, 116.6, 56.5, 56.3, 48.9, 48.8, 45.8, 42.6, 41.9, 26.4, 25.7; MS (CI)  $m/z$  248.3 ( $M + H$ ). The dihydrochloride salt was prepared by dissolving the title compound in ethyl acetate and adding 3N HCl in ethyl acetate.

Unless otherwise indicated, the procedure described in Example 20 was used to prepare the title compounds of Examples 21 through 26.

Example 21

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-CYANO-PHENYL ESTER

4-Cyanophenol was used. The title compound was prepared in 18% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.64 (d, 2H,  $J = 7.9$  Hz), 7.24 (dd, 2H,  $J = 8.7, 3.7$  Hz), 4.41-4.39 (m, 1H, major), 4.34-4.33 (m, minor), 3.79 (t,  $J = 5.8$  Hz, minor), 3.72 (t, 2H,  $J = 5.8$  Hz, major), 3.15-2.96 (m, 6H), 2.07-2.02 (m, 2H), 1.79-1.69 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  155.1, 155.0, 152.9, 152.1, 133.74, 133.70, 122.94,

122.90, 118.71, 118.68, 109.1, 109.0, 57.4, 57.1, 49.5, 49.3, 46.5, 46.4, 43.6, 43.2, 27.6, 26.8; GCMS m/z 271 (M). The hydrochloride salt was prepared; m.p. = 289.8°C.

Example 22

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-BENZYLOXY-PHENYL

5

ESTER

4-Benzyloxyphenol was used. The title compound was prepared in 4% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.44-7.31 (m, 5H), 7.04-6.99 (m, 2H), 6.97-6.93 (m, 2H), 5.04 (s, 2H), 4.51-4.49 (m, 1H, major), 4.45-4.44 (m, minor), 3.89 (t, J = 5.8 Hz, minor), 3.80 (t, 2H, J = 5.8 Hz, major), 3.27-3.08 (m, 6H), 2.20-2.10 (m, 2H), 1.86-1.76 (m, 2H); GCMS m/z 352 (M). The hydrochloride salt was prepared; m.p. = 278.5°C.

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Example 23

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-CYCLOHEXYL-PHENYL

ESTER

4-Cyclohexylphenol was used. The title compound was prepared in 18% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.17 (d, 2H, 8.3 Hz), 7.01 (dd, 2H, J = 8.7, 2.5 Hz), 4.45-4.43 (m, 1H, major), 4.38-4.36 (m, minor), 3.82 (t, J = 5.8 Hz, minor), 3.75 (t, 2H, J = 5.8 Hz, major), 3.18-3.00 (m, 6H), 2.51-2.45 (m, 1H), 2.13-2.04 (m, 2H), 1.86-1.68 (m, 6H), 1.40-1.35 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 154.4, 153.7, 149.6, 149.5, 145.3, 145.2, 127.81, 127.77, 121.6, 57.6, 57.3, 49.0, 48.9, 46.6, 46.5, 44.2, 43.2, 42.9, 34.8, 27.5, 27.4, 27.1, 26.7, 26.4; GCMS m/z 328 (M). The hydrochloride salt was prepared; m.p. = 294.1°C.

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Example 24

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-METHYLSULFANYL-PHENYL

ESTER

4-Methylthiophenol was used. The title compound was prepared in 11 % yield as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.25 (d, 2H, J = 8.7 Hz), 7.05-7.02 (m, 2H), 4.43-4.42 (m, 1H, major), 4.36-4.35 (m, minor), 3.81 (t, J = 5.8 Hz, minor), 3.73 (t, 2H, J = 5.8 Hz, major), 3.16-2.96 (m, 6H), 2.45 (s, 3H), 2.11-2.02 (m, 2H), 1.78-1.67 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 154.1, 153.4, 149.5, 149.4, 135.1, 134.9, 128.4, 122.5, 57.5, 57.2, 49.1, 49.0, 46.5, 46.4, 43.3, 43.0, 27.5, 26.8, 16.9; MS (CI) m/z 293.3 (M + H). The hydrochloride salt was prepared; m.p. = 235.2 °C.

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Example 25

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-INDAN-1-YL-PHENYL ESTER

4-(1-Indanyl)phenol was used. The title compound was prepared in 18% yield as a yellow oil: MS (CI) m/z 363.3 (M + H). The hydrochloride salt was prepared; m.p. = 168.7 °C.

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Example 26

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-iodo-PHENYL ESTER

4-Iodophenol was used. The title compound was prepared in 34% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.64 (d, 2H, 8.7 Hz), 6.90-6.86 (m, 2H), 4.41-4.39 (m, 1H, major), 4.34-4.33 (m, minor), 3.79 (t, J = 5.8 Hz, minor), 3.72 (t, 2H, J = 5.8 Hz, major), 3.15-2.95 (m, 6H), 2.09-2.02 (m, 2H), 1.77-1.67 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.7, 152.9, 151.6, 151.5, 138.5, 138.4, 124.2, 89.3, 89.2, 57.6, 57.2, 49.3, 49.1, 46.5, 46.4, 43.5, 43.2, 27.6, 26.9; GCMS m/z 372 (M). The hydrochloride salt was prepared; m.p. = 280.2°C.

Example 27

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-BENZOYL-PHENYL ESTER

Phosgene (1.22 mL, 2.3 mmol, 20% in  $\text{PhCH}_3$ ) was slowly added to a solution of 4-hydroxybenzophenone (440 mg, 2.2 mmol) and  $\text{Et}_3\text{N}$  (280  $\mu\text{L}$ , 4.0 mmol) in  $\text{PhCH}_3$  (10.0 mL) at RT. The mixture was stirred for a period of 3 h.  $\text{Et}_3\text{N}$  (280  $\mu\text{L}$ , 4.0 mmol), polymer supported DMAP (140 mg, 0.2 mmol) and 1,4-diaza-bicyclo[3.2.2]nonane (256 mg, 2.0 mmol) were added. The mixture was allowed to stir for 2 h. at RT and then was heated to 100 °C for 16 h. The reaction mixture was allowed to cool to RT, filtered and  $\text{CHCl}_3$  (40 mL) was added. The organics were washed with  $\text{H}_2\text{O}$  (10 mL x 2) and brine (10 mL) and then dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The crude residue was purified by chromatography (Biotage 40M column) eluting with 5% MeOH in  $\text{CHCl}_3$  containing 20 drops of  $\text{NH}_4\text{OH}$  per liter of eluent to afford 116 mg (15% yield) of the title compound as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.83 (d, 2H, J = 8.7 Hz), 7.78 (d, 2H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 7.26-7.22 (m, 2H), 4.48-4.47 (m, 1H, major), 4.41-4.40 (m, minor), 3.86 (t, J = 5.8 Hz, minor), 3.78 (t, 2H, J = 5.8 Hz), 3.20-3.02 (m, 6H), 2.14-2.08 (m, 2H), 1.83-1.73 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  195.9, 155.0, 154.9, 153.4, 152.6, 137.9, 134.7, 134.6, 132.6, 131.84, 131.81, 130.2, 128.5, 121.74, 121.72, 57.4, 57.1, 49.2, 49.1, 46.5, 46.4, 43.2, 42.9, 27.4, 26.6; MS (CI) m/z 351.3 (M + H). The hydrochloride salt was prepared by dissolving the title compound in ethyl acetate and adding 3N HCl in ethyl acetate; m.p. = 236. °C.

Unless otherwise indicated, the procedure described in Example 27 was used to prepare the title compounds of Examples 28 through 65.

Example 28

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-BENZYL-PHENYL ESTER

4-Benzylphenol was used. The title compound was prepared in 7% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.26-7.24 (m, 2H), 7.20-7.14 (m, 5H), 7.02-7.00 (m, 2H), 4.48-4.38 (m, 2H), 3.95 (s, 1H), 3.86 (t, 2H, J = 5.8 Hz,

major), 3.77 (t, J = 5.8 Hz), 3.16-2.93 (m, 6H), 2.10-2.03 (m, 2H), 1.78-1.67 (m, 2H); MS (CI) m/z 337.3 (M + H). The hydrochloride salt was prepared; m.p. = 221.8°C.

Example 29

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-TERT-BUTYL-PHENYL

ESTER

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4-tert-butylphenol was used. The title compound was prepared in 40% yield as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.36 (d, 2H, J = 8.7 Hz), 7.02 (d, 2H, J = 8.7 Hz), 4.49-4.48 (m, minor), 4.43-4.42 (m, 1H, major), 3.87 (t, J = 5.8 Hz, minor), 3.78 (t, 2H, J = 5.8 Hz, major), 3.23-3.02 (m, 6H), 2.15-2.02 (m, 2H), 1.83-1.67 (m, 2H), 1.30 (s, 9H); MS (CI) m/z 303.3 (M + H). The hydrochloride salt was prepared; m.p. = 289.7 °C.

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Example 30

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-IMIDAZOL-1-YL-PHENYL

ESTER

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1-(4-Hydroxyphenyl)imidazole was used. The title compound was prepared in 27% yield as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.77 (s, 1H), 7.35 (d, 2H, J = 8.7 Hz), 7.23-7.18 (m, 4H), 4.45-4.44 (m, 1H, major), 4.37-4.35 (m, minor), 3.83 (t, J = 5.8 Hz, minor), 3.74 (t, 2H, J = 5.8 Hz, major), 3.16-2.97 (m, 6H), 2.12-2.02 (m, 2H), 1.81-1.70 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 153.8, 153.0, 150.8, 150.7, 135.9, 134.7, 134.6, 130.5, 123.4, 122.81, 122.77, 118.7, 57.4, 57.1, 49.2, 49.1, 46.44, 46.37, 43.3, 43.0, 27.4, 26.7; MS (CI) m/z 313.3 (M + H). The dihydrochloride salt was prepared; m.p. > 300°C.

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Example 31

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-PHENOXY-PHENYL ESTER

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4-Hydroxy-phenoxyphenol was used. The title compound was prepared in 19% yield as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.31 (t, 2H, J = 7.5 Hz), 7.08-7.00 (m, 3H), 7.00-6.97 (m, 4H), 4.44-4.42 (m, 2H), 3.87 (t, 2H, J = 5.8 Hz, major), 3.78 (t, J = 5.8 Hz, minor), 3.27-2.93 (m, 6H), 2.15-2.02 (m, 2H), 1.87-1.69 (m, 2H); MS (CI) m/z 339.3 (M + H). The hydrochloride salt was prepared; m.p. = 238.0°C.

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Example 32

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-TRIFLUOROMETHYL-PHENYL ESTER

4-(Trifluoromethyl)phenol was used. The title compound was prepared in 18% yield as an oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.62 (d, 2H, J = 8.3 Hz), 7.26-7.22 (m, 2H), 4.47-4.46 (m, minor), 4.41-4.40 (m, 1H, major), 3.86 (t, J = 5.8 Hz, minor), 3.77 (t, 2H, J = 5.8 Hz, major), 3.22-3.02 (m, 6H), 2.15-2.06 (m, 2H), 1.85-1.75 (m, 2H); MS (CI) m/z 315.3 (M + H). The hydrochloride salt was prepared; m.p. = 260.7°C.

Example 33

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2-BROMO-PHENYL ESTER

2-Bromophenol was used. The title compound was prepared in 35% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.57 (dt, 1H, J = 7.9, 1.5 Hz), 7.31 (td, 1H, J = 7.9, 1.5 Hz), 7.21 (td, 1H, J = 7.9, 1.7 Hz), 7.08 (td, 1H, J = 7.9, 1.5 Hz), 4.54-4.52 (m, 1H, major), 4.36-4.34 (m, minor), 3.90 (t, J = 5.8 Hz, minor), 3.77 (t, 2H, J = 5.8 Hz, major), 3.19-3.00 (m, 6H), 2.25-2.08 (m, 2H), 1.81-1.70 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.0, 152.3, 149.0, 148.9, 133.4, 133.3, 128.6, 127.0, 124.5, 124.3, 116.8, 116.7, 57.6, 57.3, 49.4, 49.3, 46.6, 46.5, 43.5, 43.1, 27.5, 26.6; MS (CI) m/z 325.2 (M + H), 327.2. The hydrochloride salt was prepared; m.p. = 267.2°C.

Example 34

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2-CHLORO-PHENYL ESTER

2-Chlorophenol was used. The title compound was prepared in 17% yield as an oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.41 (d, 1H, J = 8.3 Hz), 7.28-7.13 (m, 3H), 4.53-4.52 (m, minor), 4.42-4.41 (m, 1H, major), 3.91 (t, J = 5.8 Hz, minor), 3.86 (t, 2H, J = 5.8 Hz), 3.22-2.92 (m, 6H), 2.25-2.01 (m, 2H), 1.83-1.67 (m, 2H); MS (CI) m/z 281.3 (M + H), 283.3. The hydrochloride salt was prepared; m.p. = 251.2°C.

Example 35

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2-iodo-PHENYL ESTER

2-Iodophenol was used. The title compound was prepared in 21% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.79 (ddd, 1H, J = 7.9, 3.6, 1.5 Hz), 7.34 (t, 1H, J = 7.9 Hz), 7.18 (td, 1H, J = 7.9, 1.2 Hz), 6.94 (td, 1H, J = 7.5, 1.2 Hz), 5.8-5.6 (m, minor), 4.4-4.3 (m, 1H, major), 3.92 (t, 2H, J = 5.8 Hz, major), 3.78 (t, J = 5.8 Hz, minor), 3.20-3.02 (m, 6H), 2.28-2.10 (m, 2H), 1.83-1.70 (m, 2H); MS (CI) m/z 373.2 (M + H). The hydrochloride salt was prepared; m.p. = 254 °C.

Example 36

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4'-CYANO-BIPHENYL-4-YL  
ESTER

4'-Cyano-4-biphenol was used. The title compound was prepared in 32% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.71 (d, 2H, J = 8.3 Hz), 7.65 (d, 2H, J = 8.7 Hz), 7.57 (dd, 2H, J = 6.6, 2.0 Hz), 7.25-7.22 (m, 2H), 4.52-4.51 (m, minor), 4.44-4.43 (m, 1H, major), 3.91-3.77 (m, 2H), 3.21-2.94 (m, 6H), 2.16-2.04 (m, 2H), 1.86-1.71 (m, 2H); MS (CI) m/z 348.3 (M + H). The hydrochloride salt was prepared; m.p. > 300°C.

Example 37

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4'-BROMO-BIPHENYL-4-YL  
ESTER

4-(4'-Bromophenyl)phenol was used. The title compound was prepared in 10% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.55-7.51 (m, 4H), 7.43-7.39 (m, 2H), 7.19-7.16 (m, 2H), 4.51-4.50 (m, minor), 4.42-4.41 (m, 1H, major), 3.86 (t, 2H, J = 5.8 Hz, major), 3.77 (t, J = 5.8 Hz, minor), 3.22-2.92 (m, 6H), 2.14-2.00 (m, 2H), 1.84-1.66 (m, 2H); MS (CI) m/z 401.2 (M + H), 403.2. The hydrochloride salt was prepared; m.p. > 300°C.

Example 38

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-BENZOYLOXY-PHENYL  
ESTER

4-Hydroxyphenyl benzoate was used. The title compound was prepared in 44% yield as and oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 8.17 (d, 2H, J = 7.5 Hz), 7.64-7.60 (m, 1H), 7.49 (t, 2H, J = 7.7 Hz), 7.39 (t, 1H, J = 8.6 Hz), 7.09-7.04 (m, 3H), 4.47-4.33 (m, 1H), 3.88-3.72 (m, 2H), 3.17-2.95 (m, 6H), 2.10-2.00 (m, 2H), 1.78-1.65 (m, 2H); MS (CI) m/z 367.3 (M + H). The hydrochloride salt was prepared.

Example 39

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-[1,2,4]TRIAZOL-1-YL-  
PHENYL ESTER

4-(1-H-1,2,4-triazol-1-yl)phenol was used. The title compound was prepared in 13% yield as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 8.51 (s, 1H), 8.08 (s, 1H), 7.65 (d, 2H, J = 8.4 Hz), 7.27-7.23 (m, 2H), 4.46-4.44 (m, 1H, major), 4.38-4.36 (m, minor), 3.84 (t, J = 5.8 Hz, minor), 3.75 (t, 2H, J = 5.8 Hz, major), 3.18-2.98 (m, 6H), 2.13-2.03 (m, 2H), 1.81-1.71 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 153.7, 152.8, 151.3, 151.2, 141.2, 134.3, 134.2, 123.4, 121.32, 121.28, 57.4, 57.1, 49.3, 49.1, 46.5, 46.4, 43.3, 43.0, 27.5, 26.7; MS (CI) m/z 314.3 (M + H). The hydrochloride salt was prepared; m.p. = 253.1°C.

Example 40

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-TRIFLUORO-METHOXY-PHENYL ESTER

4-(Trifluoromethoxy)phenol was used. The title compound was prepared in 33% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.21-7.12 (m, 4H), 4.43-4.42 (m, 1H, major), 4.37-4.35 (m, minor), 3.82 (t,  $J = 5.8$  Hz, minor), 3.74 (t, 2H,  $J = 5.8$  Hz, major), 3.18-2.98 (m, 6H), 2.11-2.04 (m, 2H), 1.80-1.70 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.8, 153.0, 150.0, 149.9, 146.4, 123.2, 122.22, 122.19, 121.9, 119.4, 57.5, 57.2, 49.2, 49.1, 46.5, 46.4, 43.3, 43.0, 27.5, 26.7; MS (CI),  $m/z$  331.2 ( $M + H$ ). The hydrochloride salt was prepared; m.p. = 261.6°C.

Example 41

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-(4-ACETYL-PIPERAZIN-1-YL)-PHENYL ESTER

1-Acetyl-4-(4-hydroxyphenyl)piperazine was used. The title compound was prepared in 44% yield as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  6.99-6.96 (m, 2H), 6.88-6.84 (m, 2H), 4.41-4.40 (m, 1H, major), 4.32-4.31 (m, minor), 3.80-3.55 (m, 10H), 3.11-2.94 (m, 6H), 2.08 (s, 3H), 2.08-2.02 (m, 2H), 1.76-1.65 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  169.5, 154.6, 153.8, 148.8, 148.7, 145.4, 145.3, 122.5, 117.9, 58.2, 57.3, 57.1, 50.6, 50.5, 50.1, 48.9, 48.7, 46.4, 46.3, 46.2, 42.9, 42.6, 41.6, 27.2, 26.5, 21.5, 18.5; MS (CI)  $m/z$  373.4 ( $M + H$ ). The dihydrochloride salt was prepared; m.p. = 166.6 °C.

Example 42

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2-TRIFLUOROMETHYL-PHENYL ESTER

2-(Trifluoromethyl)phenol was used. The title compound was prepared in 25% yield as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.60 (d, 1H,  $J = 7.9$  Hz), 7.53 (br t, 1H,  $J = 7.9$  Hz), 7.32-7.24 (m, 2H), 4.44-4.30 (m, 1H), 3.84-3.72 (m, 2H), 3.15-2.91 (m, 6H), 2.13-1.98 (m, 2H), 1.78-1.64 (m, 2H); MS (CI)  $m/z$  315.3 ( $M + H$ ). The hydrochloride salt was prepared; m.p. = 228.7°C.

Example 43

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2-BENZOOXAZOL-2-YL-PHENYL ESTER

2-(o-Hydroxyphenyl)benzoxazole was used. The title compound was prepared in 35% yield as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  8.22-8.19 (m, 1H), 7.73-7.66 (m, 1H), 7.55-7.42 (m, 2H), 7.41-7.30 (m, 4H), 4.71-4.69 (m, 1H, major), 4.33-4.30 (m, minor), 3.99 (t,  $J = 5.8$  Hz, minor), 3.74 (t, 2H,  $J = 5.8$  Hz, major), 3.4-2.7 (m, 6H), 2.35-2.00 (m, 2H), 1.81-1.68 (m, 2H); MS (CI)  $m/z$  364.2 ( $M + H$ ). The hydrochloride salt was prepared; m.p. = 259.9°C.



Example 44

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2-BENZOTHAZOL-2-YL-PHENYL ESTER

2-(2-Hydroxyphenyl)benzothiazole was used. The title compound was prepared in 23% yield as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  8.26-7.90 (m, 4H), 7.52-7.47 (m 1H), 7.42-7.34 (m, 2H), 7.27-7.22 (m, 1H), 4.74-4.73 (m, minor), 4.41-3.39 (m, 1H, major), 4.04 (t, 2H, J = 5.8 Hz, major), 3.79 (t, J = 5.8 Hz, minor), 3.28-3.05 (m, 6H), 2.27-2.02 (m, 2H), 1.94-1.72 (m, 2H); MS (CI) m/z 380.2 (M + H). The hydrochloride salt was prepared; m.p. = 247.6°C.

Example 45

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-FLUORO-PHENYL ESTER

3-Fluorophenol was used. The title compound was prepared in 39% yield as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.31-7.25 (m, 1H), 6.91-6.85 (m, 3H), 4.41-4.39 (m, 1H, major), 4.35-4.33 (m, minor), 3.79 (t, J = 5.8 Hz, minor), 3.72 (t, 2H, J = 5.8 Hz, major), 3.14-2.95 (m, 6H), 2.09-2.00 (m, 2H), 1.77-1.68 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  164.3, 161.8, 153.6, 152.8, 152.6, 152.5, 152.4, 130.22, 130.17, 130.13, 130.07, 117.74, 117.72, 112.6, 112.5, 112.4, 112.3, 110.2, 110.1, 109.93, 109.91, 57.5, 57.2, 49.2, 49.1, 46.4, 46.3, 43.3, 43.0, 27.4, 26.7; MS (CI) m/z 265.3 (M + H). The hydrochloride salt was prepared; m.p. = 228.2°C.

Example 46

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-CHLORO-PHENYL ESTER

3-Chlorophenol was used. The title compound was prepared in 34% yield as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.30-7.25 (m, 1H), 7.19-7.14 (m, 2H), 7.04-7.01 (m, 2H), 4.44-4.41 (m, 1H, major), 4.39-4.36 (m, minor), 3.82 (t, J = 5.8 Hz, minor), 3.75 (t, 2H, J = 5.8 Hz, major), 3.19-3.00 (m, 6H), 2.13-2.04 (m, 2H), 1.81-1.71 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.6, 152.8, 152.2, 152.1, 134.7, 130.2, 130.1, 125.8, 125.7, 122.7, 120.4, 57.4, 57.2, 49.1, 49.0, 46.5, 46.4, 43.2, 42.9, 27.4, 26.6; MS (CI) m/z 281.2 (M + H). The hydrochloride salt was prepared; 198.3 °C.

Example 47

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-BROMO-PHENYL ESTER

3-Bromophenol was used. The title compound was prepared in 27% yield as a white solid: MS (CI) m/z 325.1 (M + H), 327.1. The hydrochloride salt was prepared; m.p. = 224.5°C.

Example 48

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-METHOXY-PHENYL ESTER

2-Methoxyphenol was used. The title compound was prepared in 29% yield as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.21-7.02 (m, 2H),

6.98-6.85 (m, 2H), 4.45-4.44 (m, 1H, major), 4.35-4.34 (m, minor), 3.80 (s, 3H), 3.80-3.70 (m, 2H), 3.20-2.97 (m, 6H), 2.20-2.03 (m, 2H), 1.78-1.62 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  154.3, 153.9, 152.1, 152.0, 141.2, 141.1, 126.6, 126.5, 123.5, 123.4, 121.0, 120.9, 112.6, 112.5, 57.6, 57.4, 56.1, 49.1, 46.54, 46.51, 43.5, 43.0, 27.3, 26.7; MS (CI)  $m/z$  277.3 (M + H).

5 The hydrochloride salt was prepared; m.p. = 204.3°C.

Example 49

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID M-TOLYL ESTER

m-Cresol was used. The title compound was prepared in 47% yield as a yellow oil:

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.22 (t, 1H, J = 7.7 Hz), 6.99 (br d, 1H, J = 7.4 Hz), 6.93-6.89 (m, 2H), 4.43-4.42 (m, 1H, major), 4.36-4.35 (m, minor), 3.80 (t, J = 5.8 Hz, minor), 3.72 (t, 2H, J = 5.8 Hz, major), 3.15-2.96 (m, 6H), 2.33 (s, 3H), 2.12-2.05 (m, 2H), 1.77-1.67 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  154.3, 153.6, 151.6, 151.5, 139.6, 139.5, 129.23, 129.18, 126.3, 126.2, 122.6, 118.9, 57.6, 57.3, 49.1, 49.0, 46.6, 46.5, 43.4, 43.0, 27.6, 26.8, 21.5; MS (CI)  $m/z$  261.3 (M + H). The hydrochloride salt was prepared; m.p. = 249.2°C.

Example 50

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-TERT-BUTYL-PHENYL ESTER

2-tert-Butylphenol was used. The title compound was prepared in 63% yield as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.33 (dd, 1H, J = 7.9, 1.7 Hz), 7.09 (br t, 1H, J = 7.5 Hz), 7.09 (br t, 1H, J = 7.9 Hz), 6.98-6.93 (m, 1H), 4.50-4.49 (m, minor), 4.37-4.36 (m, 1H, major), 3.86 (t, 1H, J = 5.8 Hz, major), 3.76 (t, J = 5.8 Hz, minor), 3.20-2.93 (m, 6H), 2.14-2.00 (m, 2H), 1.80-1.66 (m, 2H), 1.33 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  154.5, 153.6, 150.3, 149.9, 141.3, 127.21, 127.17, 127.1, 127.0, 125.5, 125.4, 124.7, 124.2, 57.7, 56.9, 50.5, 49.0, 48.8, 46.4, 46.3, 43.1, 42.9, 34.7, 34.6, 30.5, 27.5, 26.6; MS (CI)  $m/z$  303.3 (M + H). The hydrochloride salt was prepared; m.p. = 283.4°C.

Example 51

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-TRIFLUOROMETHYL-PHENYL ESTER

3-(Trifluoromethyl)phenol was used. The title compound was prepared in 42% yield as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.48-7.42 (m, 2H), 7.38-7.36 (m, 1H), 7.31-7.29 (m, 1H), 4.44-4.42 (m, 1H, major), 4.36-4.34 (m, minor), 3.82 (t, J = 5.8 Hz, minor), 3.73 (t, 1H, J = 5.8 Hz, major), 3.15-2.96 (m, 6H), 2.12-2.02 (m, 2H), 1.80-1.70 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.6, 152.8, 151.7, 151.6, 130.1, 130.0, 125.6, 122.32, 122.29, 122.22, 122.19, 119.29, 119.25, 119.21, 119.17, 57.3, 57.0,

49.2, 49.1, 46.3, 46.2, 43.2, 42.9, 27.3, 26.6; MS (CI) m/z 315.2 (M + H). The hydrochloride salt was prepared; m.p. = 229.3°C.

Example 52

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2-BENZYL-PHENYL ESTER

5        2-Benzylphenol was used. The title compound was prepared in 22% yield as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.28-7.23 (m, 4H), 7.20-7.10 (m, 5H), 4.31-4.30 (m, 1H, major), 4.22-4.21 (m, minor), 3.97 (s, 2H), 3.72 (t, 2H, J = 5.8 Hz, major), 3.63 (t, J = 5.8 Hz, minor), 3.12-2.89 (m, 6H), 2.01-1.94 (m, 2H), 1.72-1.60 (m, 2H); MS (CI) m/z 337.3 (M + H). The hydrochloride salt was prepared; m.p. = 214.  
10       °C.

Example 53

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-iodo-PHENYL ESTER

3-Iodophenol was used. The title compound was prepared in 33% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.54-7.49 (m, 2H),  
15       7.12-7.06 (m, 2H), 4.43-4.39 (m, 1H), 3.93 (t, J = 5.8 Hz, minor), 3.76 (t, 2H, J = 5.8 Hz, major), 3.17-3.06 (m, 6H), 2.12-2.02 (m, 2H), 1.82-1.72 (m, 2H); MS (CI) m/z 373.1 (M + H). The hydrochloride salt was prepared; m.p. = 243.8°C.

Example 54

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID O-TOLYL ESTER

20       2-Cresol was used. The title compound was prepared in 39% yield as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.18 (t, 2H, J = 7.9 Hz), 7.09 (d, 1H, J = 7.5 Hz), 7.04 (t, 1H, J = 7.5 Hz), 4.48-4.46 (m, 1H, major), 4.36-4.35 (m, minor), 3.86 (t, J = 5.8 Hz, minor), 3.75 (t, 2H, J = 5.8 Hz, major), 3.17-2.99 (m, 6H), 2.21 (s, 3H, major), 2.20 (s, minor), 2.16-2.05 (m, 2H), 1.79-1.69 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ  
25       153.9, 153.2, 150.2, 150.1, 131.24, 131.17, 130.6, 130.5, 127.1, 125.8, 125.7, 122.5, 122.3, 57.7, 57.3, 49.02, 48.98, 46.5, 46.4, 43.3, 42.9, 27.5, 26.8, 16.6, 16.4; MS (CI) m/z 261.3 (M + H). The hydrochloride salt was prepared; m.p. = 226.9°C.

Example 55

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-BENZOYL-PHENYL ESTER

30       3-Hydroxybenzophenone was used. The title compound was prepared in 40% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.76 (d, 2H, J = 7.1 Hz), 7.58-7.52 (m, 3H), 7.45-7.40 (m, 3H), 7.34-7.32 (m, 1H), 4.41-4.40 (m, 1H, major), 4.35-4.32 (m, minor), 3.78 (t, J = 5.8 Hz, minor), 3.70 (t, 2H, J = 5.8 Hz, major), 3.12-2.90 (m, 6H), 2.08-1.98 (m, 2H), 1.75-1.64 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ  
35       195.9, 195.8, 153.8, 153.0, 151.6, 151.5, 139.0, 138.9, 137.5, 137.4, 132.8, 130.3, 129.4, 129.3, 128.6, 127.2, 127.1, 126.3, 123.5, 123.4, 57.5, 57.2, 49.2, 49.1, 46.5, 46.4, 43.4, 43.0, 47.5, 26.7; MS (CI) m/z 351.2 (M + H). The hydrochloride salt was prepared; m.p. = 241.7°C.

Example 56

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-PHENOXY-PHENYL ESTER

3-Phenoxyphenol was used. The title compound was prepared in 24% yield as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.32-7.23 (m, 4H), 7.08 (t, 1H,  $J = 7.5$  Hz), 6.99 (d, 1H,  $J = 8.3$  Hz), 6.84-6.79 (m, 2H), 6.73-7.72 (m, 1H), 4.39-4.38 (m, 1H, major), 4.33-4.32 (m, minor), 3.85-3.68 (m, 2H), 3.08-2.88 (m, 6H), 2.07-1.97 (m, 2H), 1.76-1.65 (m, 2H); MS (CI)  $m/z$  339.3 (M + H). The hydrochloride salt was prepared; m.p. = 204.8°C.

Example 57

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID BIPHENYL-3-YL ESTER

3-Phenylphenol was used. The title compound was prepared in 17% yield as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.59-7.55 (m, 2H), 7.44-7.40 (m, 3H), 7.36-7.32 (m, 3H), 7.13-7.09 (m, 1H), 4.50-4.49 (m, 1H, major), 4.42-4.41 (m, minor), 3.87 (t,  $J = 5.8$  Hz, minor), 3.78 (t, 2H,  $J = 5.8$  Hz, major), 3.19-3.02 (m, 6H), 2.17-2.07 (m, 2H), 1.81-1.72 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  152.0, 151.9, 142.9, 140.6, 129.8, 129.7, 129.0, 128.3, 127.8, 127.4, 127.3, 124.3, 124.2, 122.2, 120.8, 57.6, 57.3, 49.1, 49.0, 46.6, 46.5, 43.2, 42.9, 27.5, 26.7; MS (CI)  $m/z$  323.3 (M + H). The hydrochloride salt was prepared; m.p. = 241. °C.

Example 58

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-NITRO-PHENYL ESTER

3-Nitrophenol was used. The title compound was prepared in 13% yield as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  8.07-8.04 (m, 1H), 8.02-7.99 (m, 1H), 7.55-7.47 (m, 2H), 4.45-4.43 (m, 1H, major), 4.37-4.36 (m, minor), 3.83 (t,  $J = 5.8$  Hz, minor), 3.75 (t, 2H,  $J = 5.8$  Hz, major), 3.18-2.98 (m, 6H), 2.13-2.03 (m, 2H), 1.82-1.71 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.2, 152.1, 148.9, 130.1, 130.0, 128.6, 120.4, 120.3, 117.7, 57.4, 57.1, 49.5, 49.3, 46.5, 46.4, 43.5, 43.2, 27.5, 26.7; MS (CI)  $m/z$  292.3 (M + H). The hydrochloride salt was prepared; m.p. = 205.1°C.

Example 59

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-BROMO-3,5-DIMETHYL-PHENYL ESTER

4-Bromo-3,5-dimethylphenol was used. The title compound was prepared in 29% yield as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  6.86 (d, 2H,  $J = 5.0$  Hz), 4.42-4.41 (m, 1H, major), 4.37-4.36 (m, minor), 3.81 (t,  $J = 5.8$  Hz, minor), 3.74 (t, 2H,  $J = 5.8$  Hz, major), 3.18-3.00 (m, 6H), 2.39 (s, 6H), 2.12-2.04 (m, 2H), 1.80-1.71 (m, 2H); MS (CI)  $m/z$  353.1 (M + H), 355.1. The hydrochloride salt was prepared; m.p. = 239.5 °C.

Example 60

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-BROMO-3-METHYL-PHENYL  
ESTER

4-Bromo-3-methylphenol was used. The title compound was prepared in 41% yield  
5 as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.48 (d, 1H,  $J = 8.3$  Hz), 7.01 (dd, 1H,  $J = 4.8, 2.7$  Hz), 6.84-6.80 (m, 1H), 4.43-4.41 (m, 1H, major), 4.37-4.35 (m, minor), 3.81 (t,  $J = 5.8$  Hz, minor), 3.74 (t, 2H,  $J = 5.8$  Hz, major), 2.37 (s, 3H), 2.12-2.02 (m, 2H), 1.80-1.70 (m, 2H); MS (CI)  $m/z$  339.1 (M + H), 341.1. The hydrochloride salt was prepared; m.p. = 212.5°C.

Example 61

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-BROMO-3-CHLORO-  
PHENYL ESTER

4-Bromo-3-chlororphenol was used. The title compound was prepared in 61% yield  
15 as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.56 (dd, 1H,  $J = 8.7, 1.0$  Hz), 7.28-7.26 (m, 1H), 6.95-6.91 (m, 1H), 4.39-4.37 (m, 1H, major), 4.33-4.31 (m, minor), 3.77 (t,  $J = 5.8$  Hz, minor), 3.72 (t, 2H,  $J = 5.8$  Hz), 3.15-2.95 (m, 6H), 2.08-2.01 (m, 2H), 1.78-1.68 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.3, 152.5, 151.2, 151.1, 134.9, 134.8, 134.0, 133.9, 124.3, 122.0, 118.7, 118.6, 57.5, 57.2, 49.4, 49.2, 46.5, 46.4, 43.5, 43.2, 27.6, 26.8; MS (CI)  $m/z$  359.0 (M + H), 361.0. The hydrochloride salt was prepared; m.p. =  
20 234.7°C.

Example 62

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3,4-DIMETHYL-PHENYL  
ESTER

3,4-Dimethylphenol was used. The title compound was prepared in 46% yield as a  
25 white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.14-7.07 (m, 1H), 6.91-6.82 (m, 2H), 4.44-4.42 (m, 1H, major), 4.37-4.35 (m, minor), 3.87-3.71 (m, 2H), 3.17-2.97 (m, 6H), 2.23 (s, 3H), 2.22 (s, 3H), 2.14-2.04 (m, 2H), 1.79-1.68 (m, 2H); MS (CI)  $m/z$  275.3 (M + H). The hydrochloride salt was prepared; m.p. = 246.0°C.

Example 63

30 1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3,4-DICHLORO-PHENYL  
ESTER

3,4-Dichlorophenol was used. The title compound was prepared in 32% yield as a  
yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, mixture of conformational isomers)  $\delta$  7.40 (dd, 1H,  $J = 8.7, 1.2$  Hz), 7.28-7.25 (m, 1H), 7.02-6.97 (m, 1H), 4.40-4.38 (m, 1H, major), 4.35-4.33 (m,  
35 minor), 3.78 (t,  $J = 5.8$  Hz, minor), 3.72 (t, 2H,  $J = 5.8$  Hz, major), 3.16-2.97 (m, 6H), 2.08-2.00 (m, 2H), 1.79-1.69 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.3, 152.6, 150.4, 150.3, 132.9, 132.8, 130.74, 130.68, 129.3, 129.2, 124.3, 121.7, 57.4, 57.1, 49.4, 49.2, 46.5, 46.4,

43.4, 43.2, 27.5, 26.7; MS (CI) m/z 315.2 (M + H), 317.2. The hydrochloride salt was prepared; m.p. = 260.2°C.

Example 64

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3-PYRIDIN-3-YL-PHENYL

ESTER

3-Pyridin-3-yl-phenol (see below for preparation) was used. The title compound was prepared in 29% yield as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 8.81 (d, 1H, J = 1.6 Hz), 8.57 (dd, 1H, J = 5.0, 1.6 Hz), 7.86-7.83 (m, 1H), 7.47-7.32 (m, 4H), 7.16-7.14 (m, 1H), 4.47-4.46 (m, 1H, major), 4.38-4.37 (m, minor), 3.84 (t, J = 5.8 Hz, minor), 3.75 (t, 2H, J = 5.8 Hz, major), 3.16-2.95 (m, 6H), 2.14-2.02 (m, 2H), 1.80-1.66 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 154.0, 153.3, 152.3, 152.2, 149.0, 148.5, 139.4, 139.3, 136.0, 134.7, 130.2, 130.1, 124.3, 124.2, 123.8, 121.7, 120.9, 57.6, 57.2, 49.2, 49.1, 46.5, 46.4, 43.4, 43.1, 27.6, 26.8; MS (CI) m/z 324.3 (M + H). The dihydrochloride salt was prepared; m.p. = 210.2°C.

Example 65

3-PYRIDIN-3-YL-PHENOL HYDROBROMIDE

3-Methoxyphenylboronic acid (0.334 g, 2.2 mmol), sodium carbonate (0.848 g, 8.0 mmol) and tetrakis(triphenylphosphine) palladium (0.231 g, 0.2 mmol) were added to a flask and the flask was purged with nitrogen. Ethanol (30.0 mL) and water (1.5 mL) were added followed by 3-bromopyridine (0.316 g, 2.0 mmol). The reaction mixture was heated to 80°C for a period of 8 h. After cooling to RT, the mixture was diluted with water (5.0 mL) and extracted with ethyl acetate (20 mL x 4). The combined organic extracts were washed with brine (25 mL), dried (Na<sub>2</sub>CO<sub>3</sub>), filtered and concentrated. The crude residue was purified by chromatography (Biotage, 40S) eluting with 10% ethyl acetate in hexanes to afford 239 mg (65%) of 3-(3-Methoxy-phenyl)-pyridine as a yellow oil: MS (CI) m/z 186.1 (M + H).

The 3-(3-Methoxy-phenyl)-pyridine was treated with HBr (5 mL) at 100 °C for 12 h. The reaction mixture was allowed to cool to RT and concentrated to afford 298 mg (92%) of the title compound as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 9.14 (d, 1H, J = 2.1 Hz), 8.90-8.83 (m, 2H), 8.17 (dd, 1H, J = 8.3, 5.8 Hz), 7.39 (t, 1H, J = 8.1 Hz), 7.27-7.25 (m, 1H), 7.20-7.19 (m, 1H), 6.98-6.95 (m, 1H), 4.93 (br s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 158.7, 144.6, 140.9, 139.7, 139.6, 134.9, 130.8, 127.7, 118.3, 117.1, 114.0; GCMS m/z 171 (M).

Example 66

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-(4,4,5,5-TETRAMETHYL-[1,3,2]DIOXABOROLAN-2-YL)-PHENYL ESTER

Bis(pinacolato)diboron (0.86 g, 3.38 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) dichloromethane adduct (0.25 g, 0.308 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.17 g, 0.308 mmol), potassium acetate (0.905 g, 9.22 mmol) and 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-bromo-phenyl ester (1.00 g, 3.08 mmol) were added to a flask and purged with a stream of nitrogen. Methyl sulfoxide (15.4 mL) was added and the mixture was placed in an oil bath at 100 °C for a period of 14 h. The reaction mixture was allowed to cool to RT, diluted with ethyl acetate (15 mL) and water (15 mL). The layers were partitioned and the aqueous layer was extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with water (30 mL x 2), brine (30 mL) and dried (Na<sub>2</sub>CO<sub>3</sub>). After filtration and concentration, the crude residue was purified by chromatography (Biotage, 40M, 4% methanol/chloroform to 6% methanol/chloroform gradient) to afford 561 mg (49%) of the title compound as a brown oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) 7.80 (d, 2H, J = 7.9 Hz), 7.14-7.10 (m, 2H), 4.45-4.43 (m, 1H, major), 4.37-4.36 (m, minor), 3.82 (t, J = 5.8 Hz, minor), 3.74 (t, 2H, J = 5.8 Hz, major), 3.16-2.97 (m, 6H), 2.12-2.02 (m, 2H), 1.78-1.67 (m, 2H), 1.33 (s, 12H); MS (CI) m/z 373.3 (M + H).

Example 67

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID BIPHENYL-4-YL ESTER

1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)-phenyl ester (76.0 mg, 0.204 mmol), bromobenzene (43.0 µL, 0.408 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) dichloromethane adduct (16.7 mg, 0.0204 mmol), 1,1'-bis(diphenylphosphino)ferrocene (11.3 mg, 0.0204 mmol), and potassium phosphate (130 mg, 0.612 mmol) were added to a flask and purged with a stream of nitrogen. 1,4-Dioxane (2.46 mL) and water (122 µL) were added and the mixture was placed in an oil bath at 80°C for 20 h. The reaction mixture was allowed to cool to RT, diluted with ethyl acetate (5 mL) and water (5 mL). The layers were partitioned and the aqueous layer was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with water (10 mL x 2), brine (10 mL) and dried (Na<sub>2</sub>CO<sub>3</sub>). After filtration and concentration, the crude residue was purified by chromatography (Biotage, 12M, 4% methanol/chloroform to 6% methanol/chloroform gradient) to afford 41.6 mg (63%) of the title compound as a brown oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 7.59-7.55 (m, 4H), 7.43 (t, 2H, J = 7.9 Hz), 7.34 (t, 1H, J = 7.5 Hz), 7.22-7.17 (m, 2H), 4.48-4.47 (m, 1H, major), 4.41-4.39 (m, minor), 3.85 (t, J = 5.8 Hz, minor), 3.77 (t, 2H, J = 5.8 Hz, major), 3.19-3.00 (m, 6H), 2.16-2.05 (m, 2H), 1.81-1.70 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 154.2, 153.4, 151.2,

151.1, 140.7, 138.6, 138.5, 129.0, 128.3, 128.2, 127.5, 127.3, 123.8, 122.3, 57.6, 57.3, 49.1, 49.0, 46.6, 46.5, 43.3, 42.9, 27.5, 26.7; GCMS m/z 322 (M). The hydrochloride salt was prepared by dissolving the title compound in ethyl acetate and adding 3N HCl in ethyl acetate.

Unless otherwise indicated, procedures analogous to the procedure described in Example 67 were used to prepare the title compounds of Examples 68 through 70.

Example 68

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-PYRIDIN-2-YL-PHENYL  
ESTER

2-Bromopyridine was used. The title compound was prepared in 60% yield as a brown oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 8.65 (d, 1H, J = 4.6 Hz), 7.98 (d, 2H, J = 8.7 Hz), 7.74-7.67 (m, 2H), 7.23-7.16 (m, 3H), 4.47-4.45 (m, 1H, major), 4.39-4.38 (m, minor), 3.84 (t, J = 5.8 Hz, minor), 3.75 (t, 2H, J = 5.8 Hz, major), 3.16-2.99 (m, 6H), 2.13-2.06 (m, 2H), 1.80-1.68 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 156.9, 154.0, 153.2, 152.4, 152.4, 149.9, 137.0, 136.7, 136.6, 131.5, 131.4, 128.6, 128.5, 128.12, 128.09, 122.3, 122.21, 122.19, 120.6, 57.5, 57.2, 49.1, 49.0, 46.5, 46.4, 43.3, 42.9, 27.5, 26.7; MS (CI) m/z 324.3 (M + H). The dihydrochloride salt was prepared.

Example 69

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-PYRIDIN-3-YL-PHENYL  
ESTER

3-Bromopyridine was used. The title compound was prepared in 72% yield as a brown oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 8.79 (s, 1H), 8.55 (d, 1H, J = 4.6 Hz), 7.81 (d, 1H, J = 8.3 Hz), 7.54 (d, 2H, J = 8.3 Hz), 7.32 (dd, 1H, J = 7.9, 5.0 Hz), 7.21 (dd, 2H, J = 8.3, 3.0 Hz), 4.46-4.45 (m, 1H, major), 4.37-4.36 (m, minor), 3.83 (t, J = 5.8 Hz, minor), 3.74 (t, 2H, J = 5.8 Hz, major), 3.16-2.98 (m, 6H), 2.11-2.02 (m, 2H), 1.78-1.67 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 154.0, 153.2, 151.8, 151.7, 148.6, 148.4, 136.2, 135.1, 135.0, 134.5, 131.5, 131.4, 128.6, 128.5, 128.3, 128.2, 123.8, 122.7, 57.5, 57.2, 49.2, 49.1, 46.5, 46.4, 43.3, 43.0, 27.5, 26.7; MS (CI) m/z 324.3 (M + H). The dihydrochloride salt was prepared.

Example 70

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-PYRIDIN-4-YL-PHENYL  
ESTER

4-Bromopyridine hydrochloride was used. The title compound was prepared in 49% yield as a brown oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, mixture of conformational isomers) δ 8.61 (br s, 2H), 7.61 (d, 2H, J = 8.3 Hz), 7.45 (d, 2H, J = 5.0 Hz), 7.23 (dd, 2H, J = 8.3, 3.5 Hz), 4.46-4.45 (m, 1H, major), 4.37-4.36 (m, minor), 3.83 (t, J = 5.8 Hz, minor), 3.74 (t, 2H, J = 5.8 Hz, major), 3.16-2.98 (m, 6H), 2.11-2.02 (m, 2H), 1.79-1.69 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 153.9, 153.1, 152.5, 152.4, 150.5, 147.8, 135.4, 135.3, 131.5, 131.4, 128.6, 128.5, 128.22,



128.17, 122.7, 121.8, 57.5, 57.2, 49.2, 49.1, 46.5, 46.4, 43.4, 43.0, 27.5, 26.7; MS (CI) m/z 324.3 (M + H). The dihydrochloride salt was prepared.

The following slightly modified procedure was used to prepare the title compounds of Examples 71 through 96.

- 5        RAM tubes were charged with aryl bromides (0.125 mmol). A solution of 1,1'-bis(diphenylphosphino)ferrocene in dioxane (2.772 mg per 0.2 mL) and a solution of 1,4-diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-(4,4,5,5-tetramethyl[1,3,2]dioxaboro-lan-2-yl)-phenyl ester in dioxane (18.6 mg per 0.7 mL dioxane) were added to each reaction tube. Next a solution of K<sub>3</sub>PO<sub>4</sub> in H<sub>2</sub>O (33.1 mg per 0.05 mL) were added with stirring. Finally,
- 10        [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) dichloromethane adduct was added as a slurry in DMF (4.08 mg per 0.05 mL). The reactions were heated at 95 °C overnight under argon with shaking to agitate. The reaction mixtures were worked up by adding water (2 mL), followed by EtOAc (4 mL, sip and spit agitation). Remove organic layer (top) and pass through an SPE cartridge with Na<sub>2</sub>SO<sub>4</sub>. Re-extract reaction with 3 mL EtOAc,
- 15        then 2 mL EtOAc and combine organic extracts and concentrate. The crude residue was purified by reverse phase HPLC using a Micromass Platform LC System with a Waters Symmetry C<sub>18</sub>, 5 µm, 30 x 150 mm column using gradient elution. Solvent A is 0.1% trifluoroacetic acid in water and Solvent B is acetonitrile. The flow rate was 20 mL/min. A linear gradient of 0-100% B over 15 min. was used and the products were collected by mass trigger (ES+) and concentrated in a GeneVac. The products were analyzed by analytical HPLC using a Waters Alliance System with a Waters Symmetry C<sub>18</sub>, 5 µm, 2.1 x 150 mm column using gradient elution. The flow rate was 0.5 mL/min. Two different gradients using the solvent systems described above were used. Method 1 (M1) used a linear gradient of 0-100% B over 10 min. Method 2 (M2) used a linear gradient of 10-100% B over 10 min.
- 20

Example 71

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2',5'-DIMETHYL-BIPHENYL-4-YL ESTER

2-Bromo-1,4-dimethylbenzene was used. The title compound was prepared in 41.3 % yield as it's trifluoroacetic acid salt: MS (ES+) m/z 351.0 (M + H), HPLC retention time (M1) = 7.416 min.

Example 72

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2'-METHOXY-BIPHENYL-4-YL ESTER

2-Bromoanisole was used. The title compound was prepared in 43.3% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 353.0 (M + H), HPLC retention time (M1) = 6.837 min.

Example 73

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-FURAN-3-YL-PHENYL ESTER

3-Bromofuran was used. The title compound was prepared in 5.2% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 313.0 (M + H), HPLC retention time (M1) = 6.330 min.

Example 74

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3'-METHOXYCARBONYL-BIPHENYL-4-YL ESTER

Methyl 3-Bromobenzoate was used. The title compound was prepared in 49.0% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 381.0 (M + H), HPLC retention time (M1) = 6.701 min.

Example 75

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-(6-FLUORO-PYRIDIN-3-YL)-PHENYL ESTER

5-Bromo-2-fluoropyridine was used. The title compound was prepared in 53.1% yield as it's bistrifluoroacetic acid salt: MS (ES+) m/z 342.0 (M + H), HPLC retention time (M1) = 6.011 min.

Example 76

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-(5-ETHOXYCARBONYL-PYRIDIN-3-YL)-PHENYL ESTER

5-Bromo-nicotinic acid ethyl ester was used. The title compound was prepared in 30.5% yield as it's bistrifluoroacetic acid salt: MS (ES+) m/z 396.0 (M + H), HPLC retention time (M2) = 4.981 min.

Example 77

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-QUINOLIN-3-YL-PHENYL ESTER

3-Bromoquinoline was used. The title compound was prepared in 28.6% yield as it's bistrifluoroacetic acid salt: MS (ES+) m/z 374.0 (M + H), HPLC retention time (M2) = 4.219 min.

Example 78

5    1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2',4',6'-TRIMETHYL-BIPHENYL-4-YL ESTER

1-Bromo-2,4,6-trimethylbenzene was used. The title compound was prepared in 2.5% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 365.1 (M + H), HPLC retention time (M2) = 7.054 min.

10    Example 79

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3'-METHYL-BIPHENYL-4-YL ESTER

m-Bromotoluene was used. The title compound was prepared in 13.3% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 337.0 (M + H), HPLC retention time (M2) = 6.435 min.

15    Example 80

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4'-CHLORO-BIPHENYL-4-YL ESTER

4-Bromochlorobenzene was used. The title compound was prepared in 25.9% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 357.0 (M + H), HPLC retention time (M2) = 6.618 min.

20    Example 81

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4'-NITRO-BIPHENYL-4-YL ESTER

1-Bromo-4-nitrobenzene was used. The title compound was prepared in 12.5% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 368.0 (M + H), HPLC retention time (M2) = 6.087 min.

Example 82

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2'-METHYL-BIPHENYL-4-YL ESTER

30    o-Bromotoluene was used. The title compound was prepared in 26.2% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 337.0 (M + H), HPLC retention time (M2) = 6.378 min.

Example 83

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2'-CHLORO-BIPHENYL-4-YL ESTER

35    2-Bromochlorobenzene was used. The title compound was prepared in 28.0% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 357.0 (M + H), HPLC retention time (M2) = 6.329 min.

Example 84

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3'-CHLORO-BIPHENYL-4-YL  
ESTER

3-Bromochlorotoluene was used. The title compound was prepared in 23.4% yield as  
5 it's trifluoroacetic acid salt: MS (ES+) m/z 357.0 (M + H), HPLC retention time (M2) = 6.558  
min.

Example 85

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2'-NITRO-BIPHENYL-4-YL  
ESTER

10 1-Bromo-2-nitrobenzene was used. The title compound was prepared in 20.8% yield  
as it's trifluoroacetic acid salt: MS (ES+) m/z 368.0 (M + H), HPLC retention time (M2) =  
5.851 min.

Example 86

15 1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3',5'-DIMETHYL-BIPHENYL-  
4-YL ESTER

1-Bromo-3,5-dimethylbenzene was used. The title compound was prepared in 15.1%  
yield as it's trifluoroacetic acid salt: MS (ES+) m/z 351.0 (M + H), HPLC retention time (M2) =  
6.802 min.

Example 87

20 1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3'-CYANO-BIPHENYL-4-YL  
ESTER

3-Bromobenzonitrile was used. The title compound was prepared in 38.1% yield as  
it's trifluoroacetic acid salt: MS (ES+) m/z 348.0 (M + H), HPLC retention time (M2) = 5.758  
min.

25 Example 88

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 2',3'-DIMETHYL-BIPHENYL-  
4-YL ESTER

1-Bromo-2,3-dimethylbenzene was used. The title compound was prepared in 17.2%  
yield as it's trifluoroacetic acid salt: MS (ES+) m/z 351.0 (M + H), HPLC retention time (M2) =  
30 6.726 min.

Example 89

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-(6-METHYL-PYRIDIN-2-YL)-  
PHENYL ESTER

2-Bromo-6-methylpyridine was used. The title compound was prepared in 35.4% yield  
35 as it's bistrifluoroacetic acid salt: MS (ES+) m/z 338.0 (M + H), HPLC retention time (M2) =  
2.086 min.

Example 90

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-(3,5-DIMETHYL-ISOXAZOL-4-YL)-PHENYL ESTER

5 4-Bromo-3,5-dimethylisoxazole was used. The title compound was prepared in 17.6% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 342.0 (M + H), HPLC retention time (M2) = 5.076 min.

Example 91

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-(4-METHYL-PYRIDIN-2-YL)-PHENYL ESTER

10 2-Bromo-4-methylpyridine was used. The title compound was prepared in 27.6% yield as it's bistrifluoroacetic acid salt: MS (ES+) m/z 338.0 (M + H), HPLC retention time (M2) = 2.805 min.

Example 92

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-(5-CARBAMOYL-PYRIDIN-3-YL)-PHENYL ESTER

15 5-Bromo-nicotinamide was used. The title compound was prepared in 20.9% yield as it's bistrifluoroacetic acid salt: MS (ES+) m/z 367.0 (M + H), HPLC retention time (M2) = 2.125 min.

Example 93

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-(5-CYANO-PYRIDIN-3-YL)-PHENYL ESTER

20 5-Bromopyridine-3-carbonitrile was used. The title compound was prepared in 45.8% yield as it's bistrifluoroacetic acid salt: MS (ES+) m/z 349.0 (M + H), HPLC retention time (M2) = 4.832 min.

Example 94

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4'-METHOXY-BIPHENYL-4-YL ESTER

25 1-Bromo-4-methoxybenzene was used. The title compound was prepared in 29.6% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 353.0 (M + H), HPLC retention time (M2) = 6.001 min.

Example 95

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 3'-NITRO-BIPHENYL-4-YL ESTER

30 1-Bromo-3-nitrobenzene was used. The title compound was prepared in 35.3% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 368.0 (M + H), HPLC retention time (M2) = 6.055 min.

Example 96

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID 4-IMIDAZO[1,2-A]PYRIDIN-3-  
YL-PHENYL ESTER

3-Bromo-imidazo[1,2-a]pyridine was used. The title compound was prepared in  
5 45.8% yield as it's trifluoroacetic acid salt: MS (ES+) m/z 363.0 (M + H), HPLC retention time  
(M2) = 2.771 min.

Example 97

1,4-DIAZA-BICYCLO[3.2.2]NONANE-4-CARBOXYLIC ACID (4-BROMO-PHENYL)-AMIDE

A flame-dried round-bottomed flask was equipped with a N<sub>2</sub> cap and magnetic stir  
10 bar. 1,4-Diaza-bicyclo[3.2.2]nonane [0.3 gm (2.38 mmol)] was dissolved in 10 ml of  
anhydrous THF and the solution was treated with 0.47 gm (2.38 mmol) p-bromophenyl-  
isocyanate. The reaction mixture was stirred at room temperature for 16 hr. The solvent was  
removed in vacuo and the residue was triturated in hot ethyl acetate (10 ml). The mixture  
was filtered hot and the solid washed with ethyl acetate. The solid was dried in vacuo. The  
15 material was converted to the HCl salt by preparation of a solution containing 1 equivalent  
HCl in methanol (18 ul acetyl chloride in 3 ml methanol) followed by addition of the free base.  
The solution was evaporated in vacuo and the residue was crystallized from ether / methanol  
to afford 54 mg (63%) of the above titled product as a white solid. mp = 228 – 231°C  
C<sub>14</sub>H<sub>18</sub>BrN<sub>3</sub>O <sup>1</sup>H NMR free base (CDCl<sub>3</sub>, 400 MHz) δ 7.37 (br.d, 2 H, J = 9 Hz), 7.25 (br.d, 2H,  
20 J = 10 Hz), 6.29 (br.s, 1H), 4.13 (br.s, 1H), 3.70 (t, 2H, J = 5Hz), 3.15 – 3.05 (br.m, 2H), 3.03  
– 2.96 (br.m, 4H), 2.08 – 2.00 (br.m, 2H), 1.81 – 1.72 (br.m, 2H) ppm. <sup>13</sup>C NMR free base  
(CDCl<sub>3</sub>, 100 MHz) δ 159.0, 138.0, 131.6, 121.4, 115.0, 57.3, 48.3, 46.0, 42.0, 27.3 ppm. Mass  
Spectrum free base (APCI) m/z = 324, 326. HRMS Calc'd for C<sub>14</sub>H<sub>18</sub> Br N<sub>3</sub>O: 324.0711,  
Found: 324.0684.